Advanced Eye Monitoring Technologies: Ready for Operational Platforms

Carey D. Balaban
Michael E. Hoffer

Development Through NIHL

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Amelioration of Acute Sequelae of Blast Induced Mild Traumatic Brain Injury by N-Acetyl Cysteine: A Double-Blind, Placebo Controlled Study

Michael E. Hoffer[1*¶], Carey Balaban[2¶], Martin D. Slade[3], Jack W. Tsao[4], Barry Hoffer[5]

- NAC developed originally as protective agent (anti-oxidant and anti-inflammatory) against NIHL in animal models
- NAC does not cross intact blood-brain-barrier, but crosses injured barrier

Development Through NIHL

- NAC efficacious in theater against mild blast-related TBI
  - Subject to clinical trials by others
- Need for better assessment of mild TBI has fostered development of goggle technologies for assessing eye movements

Prospects for Operational Monitoring of Eye and Pupil Movements

- Coordinated movements of the eyes in the orbit, lens (accommodation) and pupil are used to acquire and analyze visual information
  - Effectors are extraocular muscles, ciliary muscle and iris dilator and sphincter muscles
- Eye movements may be conjugate (both eyes move in parallel with the same magnitude and direction) or disconjugate

Prospects for Operational Monitoring of Eye and Pupil Movements

- Conjugate movements (symmetric):
  - Saccadic eye movements: ballistic orientation of fovea to new target, followed by fixation (dwell)
  - Smooth pursuit: maintain foveal fixation on slowly moving target (tracking)
  - Nystagmus: alternating fast (refixation) and slow (tracking) phase movements
    - Vestibular: slow phase compensates for head movement
    - Optokinetic: slow phase tracks peripheral optic flow

Prospects for Operational Monitoring of Eye and Pupil Movements

- Disconjugate Eye Movements (convergence and divergence)
  - Near response during convergence: Eyes converge, lens curvature increases, and pupil constricts (e.g., focus on near or approaching target)
  - Near response during divergence: Eyes diverge, lens curvature decreases, and pupil dilates (e.g., focus on far or receding target)

Prospects for Operational Monitoring of Eye and Pupil Movements

- Video-oculography permits unobtrusive monitoring of eye and pupil movements.
- Eye is imaged with digital video with infrared diode illumination
- Pupil detected and measured
- Rotation of eyeball calculated with algorithms from center of mass of pupil and iris features

Neurologic Assessment with Video-Oculography

- Eye movement motor performance dynamics (current clinical applications)
- Eye movements as components of cognitive tasks
  - Predictive saccades
  - Anti-saccade task
  - Reaction time paradigms
    - Single task
    - Dual/multitask interference
  - Gaze dwell times

Vestibular, Oculomotor and Reaction Time Assessment in the Laboratory or Office

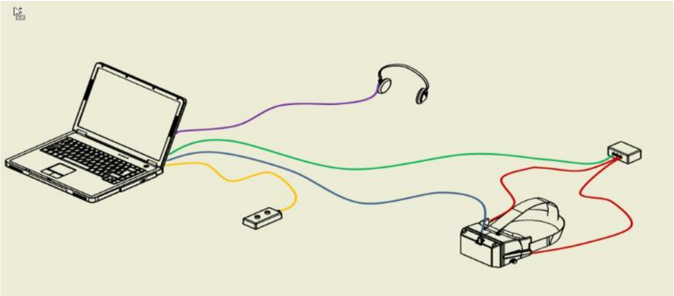
I-Portal® NOTC (Neuro-Otologic Test Center)

I-Portal ® PAS (Portable Assessment System-integrated head-mounted display and eye-tracking)

- **Purpose:**
  - Assess neuro-sensory integrity,
  - By measuring the performance of functional systems that span a broad range of neuro-sensory anatomy.
- **Oculomotor, Vestibular and Reaction Time Measures :**
  - Oculomotor Responses
  - Vestibular Performance
  - Reaction Time (Auditory, Visual and Combination- visual reaction time and oculomotor)

Hardware and Software

- Conducted with the I-PAS™ (I-Portal® Portable Assessment System, NKI Pittsburgh), a portable 3D head mounted display (HMD) system with integrated eye tracking technology.
  - Sampling rate 100 Hz
  - Resolution < 0.1°
- All stimuli are created in a virtual environment.
- Neuro Kinetics VEST™ software was used to run the battery of tests and analyze the data.



Operational Scenario for Technology

AP

US makes Cuba embassy cuts permanent after 'health attacks'

By JOSH LEDERMAN
and MATTHEW LEE
Mar. 02, 2018

https://apn

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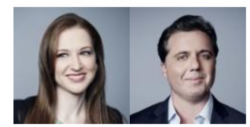
WASHINGTON (AP) — Citing mysterious "health attacks" in Havana, the United States said Friday it is making permanent its withdrawal of 60 percent of its diplomats from Cuba, extending an action that has hurt the island nation's economy and cramped Cubans' ability to visit the U.S.

Last October, the State Department ordered non-essential embassy personnel and the families of all staff to leave Havana,

US Embassy in Cuba to reduce staff indefinitely after 'health attacks'



By Laura Koran and Patrick Oppmann, CNN

Updated 6:38 PM ET, Fri March 2, 2018

The American flag flies at the U.S. Embassy following a ceremony August 14, 2015, in Havana.

Colleagues

- Carey D. Balaban (University of Pittsburgh)
- Michael E. Hoffer (University of Miami)
- Bonnie Levin (University of Miami)

Assessing Effects in Havana

- Late 2016 – 2017, reports of sudden onset dizziness, ear pain and tinnitus in diplomats and family members (no DoD personnel)
- Many reported hearing a loud, high frequency, very localized sound capable of following them in a room
- Some reported a pressure sensations localized in a room

Assessing Effects in Havana

- Over 140 individuals with suspected exposures were examined at University of Miami or in Havana, Cuba
- Identified 35 individuals with appropriate history, symptoms and perceived exposure
  - Perception of sound or pressure
  - In same room with a person with perception

Assessing Effects in Havana

- **The 35 individuals examined at University of Miami, Miller School of Medicine, 7-60 days after most recent reported exposure**
- **21 males, 14 females; 42.3 ± 11.3 years, all <64 years old**
- **Comprehensive history, physical exam which include, standard eye movement testing**
- **Specialized clinical and neuropsychological testing based on history and physical exam**
  - **Subsets received specialized testing needed to confirm a diagnosis**

Assessing Effects in Havana

- Exams of ten individuals with no symptoms were within normal limits (Unaffected Group)
  - One reported a ‘force wave’ sensation
  - One reported a single but very brief perception of high pitched sound
  - Eight were present in the same room as someone reporting an exposure

Symptom Reports

SYMPTOM	Unaffected group	Affected Group
Dizziness (Yes:No)	0:10 (0%)	23:2 (92%)*
Cognitive (Yes:No)	0:10 (0%)	14:11 (56%)*
Hearing Loss (Yes:No)	0:10 (0%)	8:17 (32%)*
Tinnitus (Yes:No)	0:10 (0%)	8:17 (32%)*
Ear Pain (Yes:No)	0:10 (0%)	7:18 (28%)*
Headache (Yes:No)	2:8 (25%)	6:19 (24%)
MULTIPLE SYMPTOMS		
At least 2 Symptoms (including HA/excluding HA, Yes:No)	0:10/0:10	24: 1/24:1**
At least 3 Symptoms (including HA/excluding HA, Yes:No)	0:10/0:10	16:9 /14:11**

*Significant difference compared to asymptomatic group, Fisher exact test, $p<0.01$

**Both values are significantly different compared to the asymptomatic group, Fisher exact test, $p<0.01$

Clinical Findings

CLINICAL FINDING (Affected Patients)		Number Tested	Abnormal	Within Normal Limits
Subjective Visual Vertical (SVV)		25	23	2
Chair Rotation HVOR		11	9	2
	Central Vestibular Findings		6	5
Antisaccade test (abnormal error rate)		23	12	11
Cervical Vestibular Evoked Myogenic Potential (cVEMP)		9	7	2
Ocular VEMP (oVEMP)		9	7	2

Cognitive and Neuropsychologic Findings

Case #	Premorbid estimate of intellect	Subjective complaints	Neuropsychological Findings
1	NART=114; High Average	• Forgetfulness • Mental fog/Slow performance • Difficulty with complex attention • Reduced motivation	• Diminished working memory • Slowed processing speed • Inefficient verbal learning • Reduced verbal fluency • Weak grip strength
2	NART=114; High Average	• Forgetfulness • Poor concentration/planning difficulty • Difficulty retrieving words • Mood swings • Increased irritability • Lack of motivation	• Mildly impaired verbal learning and memory • Mild attentional problems • Reduced word finding • Mild depression
3	NART=117; High Average	• Slower processing • Difficulty multi-tasking • Difficulty retrieving words • Greater level of effort required to complete simple tasks	• Reduced speed of processing Weak grip strength • Diminished sustained attention/ problems sustaining mental set • Difficulty making rapid visual comparisons

Abbreviation: NART- National Adult Reading Test

Cognitive and Neuropsychologic Findings

Case #	Premorbid estimate of intellect	Subjective complaints	Neuropsychological Findings
4	Average	• Slower processing • Attentional problems	• Slow processing speed
5	NART=117; High Average	• Slower processing • Difficulty concentrating • Difficulty multitasking • Feeling confused • Irritability	• Reduced ability to focus in the face of competing stimuli • Episodic memory • Attention • Working memory difficulties • Weak grip strength.
6	NART=106; Average	• Forgetfulness • Slower processing • Poor concentration • Word finding difficulties • Indecisiveness • Irritability, increased tearfulness • decreased interest in activities, anxiety & mood swings	• Difficulty with verbal memory • Reduced fine motor speed • Reduced ability to focus in the face of competing stimuli • Poor Grip Strength • Moderate depression • Mild Anxiety and apathy

Cognitive and Neuropsychologic Findings

Case #	Premorbid estimate of intellect	Subjective complaints	Neuropsychological Findings
7	NART=115; High Average	• Forgetfulness • Slower processing • Difficulty retrieving words • Mood lability & anxiety	• Decreased visual memory • Reduced verbal fluency • Weak Grip Strength
8	NART=88; Low Average	• Forgetfulness • Slower processing • Poor concentration • Difficulties with organization • Difficulty monitoring • Word finding difficulties	• Difficulty with simple verbal and visual attention, visual processing • Reduced ability to focus in the face of competing stimuli • Reduced vocabulary • Mild depression
9	Average	• Poor concentration	• Slow processing speed • Diminished abstract problem solving

Summary

- Extremely high incidence of objective signs (e.g., abnormal SVV, rotational testing and VEMPs) of underlying asymmetric vestibulopathies and otolithic abnormalities.
- Presentation more homogenous than most mTBI populations.
- Lower prevalence of headache than typical for mTBI.

Summary

- **Cognitive symptoms (e.g., problems maintaining sustained attention, slower processing speed, difficulty multi-tasking, and word retrieval difficulties) similar to mTBI or decompression sickness but more pervasive and consistently paired with emotional symptoms that included irritability, anxiety and depression.**
- **Elevated prevalence of abnormal anti-saccade task error rates.**

Source of Exposure Unknown

- **Potential directed energy sources include**
  - **Hypersonic sound**
  - **Pulsed radiofrequency**
  - **Pulsed laser source**
  - **Ultrasound (e.g., from photoacoustic device)**
- **Receiver characteristics: Waveguide, resonance and cavitation properties of intracranial contents**

Cognitive Effects of Otic Capsule Defects

Otology & Neurotology
37:70–82 © 2015, Otology & Neurotology, Inc.

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Longitudinal Cognitive and Neurobehavioral Functional Outcomes Before and After Repairing Otic Capsule Dehiscence

*P. Ashley Wackym, †Carey D. Balaban, *Heather T. Mackay, ‡Scott J. Wood, *Christopher J. Lundell, §Dale M. Carter, and ||David A. Siker

Caution re: Symptom Reports

- Causal attributions for symptoms associated with balance disorders and mTBI, including neuropsychological complaints, are unreliable.
  - Attribution obvious for overt exposure scenarios (blast wave exposure or blunt impact to the head)
  - Problematic for dizziness due to a covert cause.   For example, ear pain and cognitive symptoms are aversive so may produce conditioned aversion with misattribution.
    - Analogy to conditioned taste aversion: nausea and the symptoms may be attributed to irrelevant but novel conditions that merely coincide temporally with the proximate cause.

Neuropsychological Linkages of Balance Disorders

Pergamon

Anxiety Disorders
15 (2001) 53–79

JOURNAL OF Anxiety Disorders

Neurological bases for balance–anxiety links

Carey D. Balaban[a,*], Julian F. Thayer[b]

Neuropsychological Linkages of Balance Disorders

Journal of Vestibular Research 21 (2011) 315–321
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IOS Press

Migraine, vertigo and migrainous vertigo: Links between vestibular and pain mechanisms

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Neuropsychological Linkages of Balance Disorders

EXPERT REVIEWS

Neurologic bases for comorbidity of balance disorders, anxiety disorders and migraine: neurotherapeutic implications

Expert Rev. Neurother. 11(3), 379–394 (2011)

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The comorbidity among balance disorders, anxiety disorders and migraine has been studied extensively from clinical and basic research perspectives. From a neurological perspective, the comorbid symptoms are viewed as the product of sensorimotor, interoceptive and cognitive adaptations that are produced by afferent interoceptive information processing, a vestibulo–parabrachial nucleus network, a cerebral cortical network (including the insula, orbitofrontal cortex, prefrontal cortex and anterior cingulate cortex), a raphe nuclear–vestibular network, a coeruleo–vestibular network and a raphe–locus coeruleus loop. As these pathways overlap extensively with pathways implicated in the generation, perception and regulation of emotions and affective states, the comorbid disorders and effective treatment modalities can be viewed within the contexts of neurological and psychopharmacological sites of action of current therapies.

KEYWORDS: anxiety disorders • balance disorders • migraine • vestibular rehabilitation • vestibular system

Why is mTBI a Topic for Neurotology and Neuro-ophthalmology?

- **Balance disorders often present**
- **Co-morbidities similar to balance-migraine-anxiety**
- **Vestibular, oculomotor and reaction time tests provide objective metrics for acute mTBI**

TBI definition*

A traumatically induced structural injury and/or physiological disruption of brain function as a result of an external force that is indicated by new onset or worsening of at least one of the following clinical signs, immediately following the event:

***As developed by the Surgeon General consensus study group (DoD) May-July 2007**

TBI Definition

- **Any period of loss of or a decreased level of consciousness**
- **Any loss of memory for events immediately before or after the injury**
- **Any alteration in mental state at the time of the injury (confusion, disorientation, slowed thinking, etc)**
- **Neurological deficits**
  - **Weakness**
  - **Loss of balance**
  - **Change in vision**
  - **Praxis**
  - **Paresis/plegia**
  - **Sensory loss**
  - **Aphasia**
  - **Etc.**
- **Intracranial lesion**

Clinical Descriptors of Signs and Symptoms

- Concussion or mild TBI
- Post-concussion syndrome [310.2]
- IHS Headaches attributed to head/neck trauma
  - 5.1. Acute post-traumatic headache
  - 5.2. Chronic post-traumatic headache
  - 5.3. Acute headache attributed to whiplash injury [S13.4]
  - 5.4. Chronic headache attributed to whiplash injury [S13.4]
  - 5.5. Headache attributed to traumatic intracranial haematoma
  - 5.6. Headache attributed to other head and/or neck trauma [S06]
  - 5.7. Post-craniotomy headache
- Post-traumatic dizziness
- Post-traumatic Stress

‘Plain Language’ mTBI Definition

- **Documented traumatic event**
- **‘Not quite right’ (‘NQR’ criterion)**
- **How does one quantify ‘NQR’?**

Objective Assessment of Acute mTBI:

PLOS | ONE

RESEARCH ARTICLE

Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury

Carey Balaban[1], Michael E. Hoffer[2,3,4*], Mikhaylo Szczupak[2,4], Hillary Snapp[2], James Crawford[5], Sara Murphy[2,6], Kathryn Marshall[5], Constanza Pelusso[2,4], Sean Knowles[2], Alex Kiderman[7]

Study Populations

- Number of mTBI subjects: **100 (two successive cohorts of 50)**
- Number of Control subjects: **200 (two successive cohorts of 100)**
- Number of Testing sites: **2 (**Naval Medical Center - San Diego & Madigan Army Medical Center)

Table 1. Tests performed.

Test	Variables
Optokinetic	Left and Right Gain and Asymmetry for nystagmus beats
Smooth Pursuit–Horizontal/Vertical	Percent of Saccadic Intrusions, Initiation Time
Saccade-Random–Horizontal/Vertical	Saccade Onset Latency, Accuracy, Peak Velocity
Predictive Saccade	Point in cycle at which subject anticipates/predicts the fixed timing interval and dot position as well as percent of correct predictions
Anti-saccade Horizontal	Number of Pro-saccadic errors, correct anti-saccades, Latency, and Velocity
Self-paced Saccade	Saccades per second
Gaze Horizontal	Vertical peak and average slow phase velocity
Visual Reaction Time	Mean and Standard Deviation (SD) of Latency
Auditory Reaction Time	Mean and SD of Latency
Saccade and Reaction Time	Saccade Onset Latency, Accuracy, and Latency and SD for motor responses
Computer Controlled Rotation Head Impulse Test (crHIT)	Left and Right Gain and Asymetey
Sinusoidal Harmonic Acceleration (SHA)	Gain, Phase, and Asymmetry—High Frequencies
Visual Enhancement	Gain, Phase, and Asymmetry—High Frequencies
Visual Suppression	Gain, Phase, and Asymmetry—High Frequencies

doi:10.1371/journal.pone.0162168.t001

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Table 2. Characteristics of the subject population.

	Control Group		mTBI Group	
	Cohort 1	Cohort 2	Cohort1	Cohort 2
Gender (Females: Males)	25:75	19:81	21:29	12:38
Sample size (N)	100	100	50	50
Age (years, mean ± SD)	29.7±6.2	26.3±6.0	26.7±6.4	26.0±7.0
Symptom Score (22 item SCAT, 22 minus number symptoms, mean ± SD)	20.2±2.7	20.6±2.4	8.5±6.3	8.3±6.0
Symptom Severity (22 item SCAT, mean ± SD, max 132)	2.9±5.1	2.4±5.4	44.5±26.8	43.2±30.5
Time post-TBI (hours, mean ± SD)			58.1±35.6	66.6±39.6
Glasgow Coma Scale (mean ± SD)			15.0±0.0	14.8±1.0
Functional Gait Index (maximum 30, mean ± SD)			24.7±4.6	25.7±5.8
Dizziness Handicap Inventory Total Score (mean ± SD)			33.5±24.1	28.5±20.0
Trail Making Test A (sec, mean ± SD)			29.1±11.5	31.1±12.1
Trail Making Test B (sec, mean ± SD)			55.4±18.5	56.9±28.9

doi:10.1371/journal.pone.0162168.t002

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

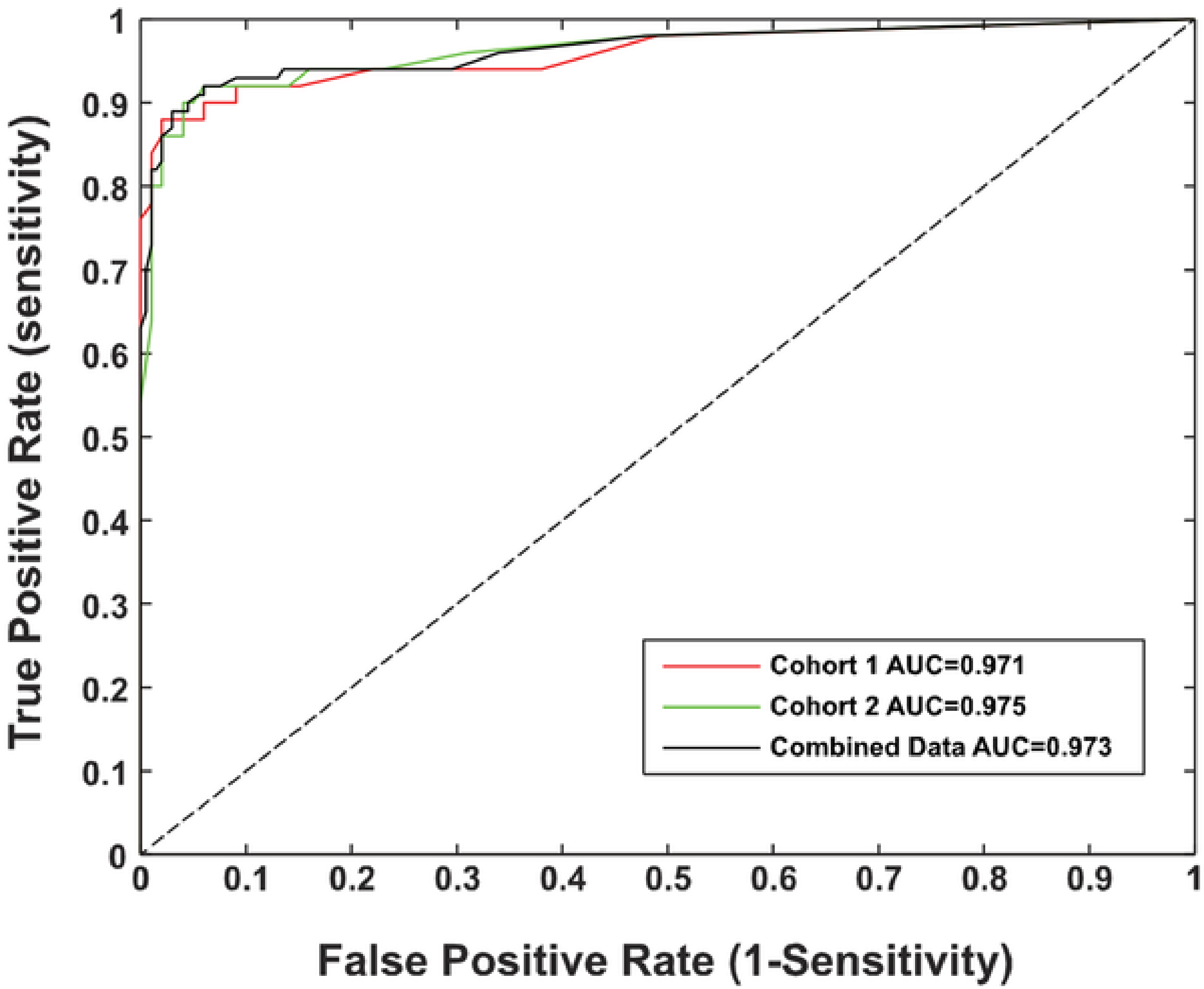
Table 3. Parameters for logistic regression models and significance levels.

	Cohort 1		Cohort 2		Combined	
Parameter (coefficient)	Estimate ± SE	Wald	Estimate ± SE	Wald	Estimate ± SE	Wald
Prosaccade error (%)	0.129±0.034	13.97***	0.107±0.028	14.91***	0.117±0.021	31.00***
crHIT absolute gain symmetry	0.824±0.231	12.79***	1.099±0.280	15.43***	0.9297±0.166	31.32***
crHIT average gain	-32.216±8.901	13.10***	-36.603±10.039	13.29***	-32.058±6.025	28.30***
Predictive Saccades (number)	-0.190±0.077	6.18*	-0.204±0.071	8.26**	-0.195±0.050	15.51***
Intercept	26.212±8.024	10.67**	30.895±8.956	11.90***	26.456±5.461	23.47***

doi:10.1371/journal.pone.0162168.t003

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Fig 1. ROC curve for Individual Cohorts and Combined Group.



Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Table 4. Sensitivities and specificities.

	True Positive (Sensitivity)	True Negative (Specificity)	Correct	ROC AUC
Cohort 1: Data	88%	99%	95.3%	0.9714
Cohort 2: Data	92%	98%	96.0%	0.9752
Combined: Data	89.0%	97.5%	94.7%	0.9727
70/30 in-out sample	90.9%	98.5%	97%	0.9765
Leave one out	87%	97%	93.7%	

doi:10.1371/journal.pone.0162168.t004

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TENTH ANNIVERSARY

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Table 5. Summary statistics for each cohort and combined group.

	Cohort 1		Cohort 2		Combined	
Variables	Control	mTBI	Control	mTBI	Control	mTBI
Prosaccade error (% responses)	12.8±12.7	**31.2±20.4**	12.8±10.5	**37.3±26.4**	12.8±11.6	**34.2±23.7**
crHIT absolute gain symmetry	1.8±1.2	**5.5±4.4**	1.6±1.3	**6.2±5.0**	1.7±1.2	**5.9±4.7**
crHIT average gain	0.96±0.04	**0.86±0.12**	0.97±0.04	**0.82±0.12**	0.96±0.04	**0.84±0.12**
Predictive Saccades (number)	14.5±4.8	**9.6±5.8**	15.4±4.1	**11.0±6.0**	14.9±4.4	**10.3±5.9**

doi:10.1371/journal.pone.0162168.t005

Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Fig 2. Cumulative distribution functions are shown for the four metrics in the logistic regression model, 89% sensitivity and 97.5% specificity.

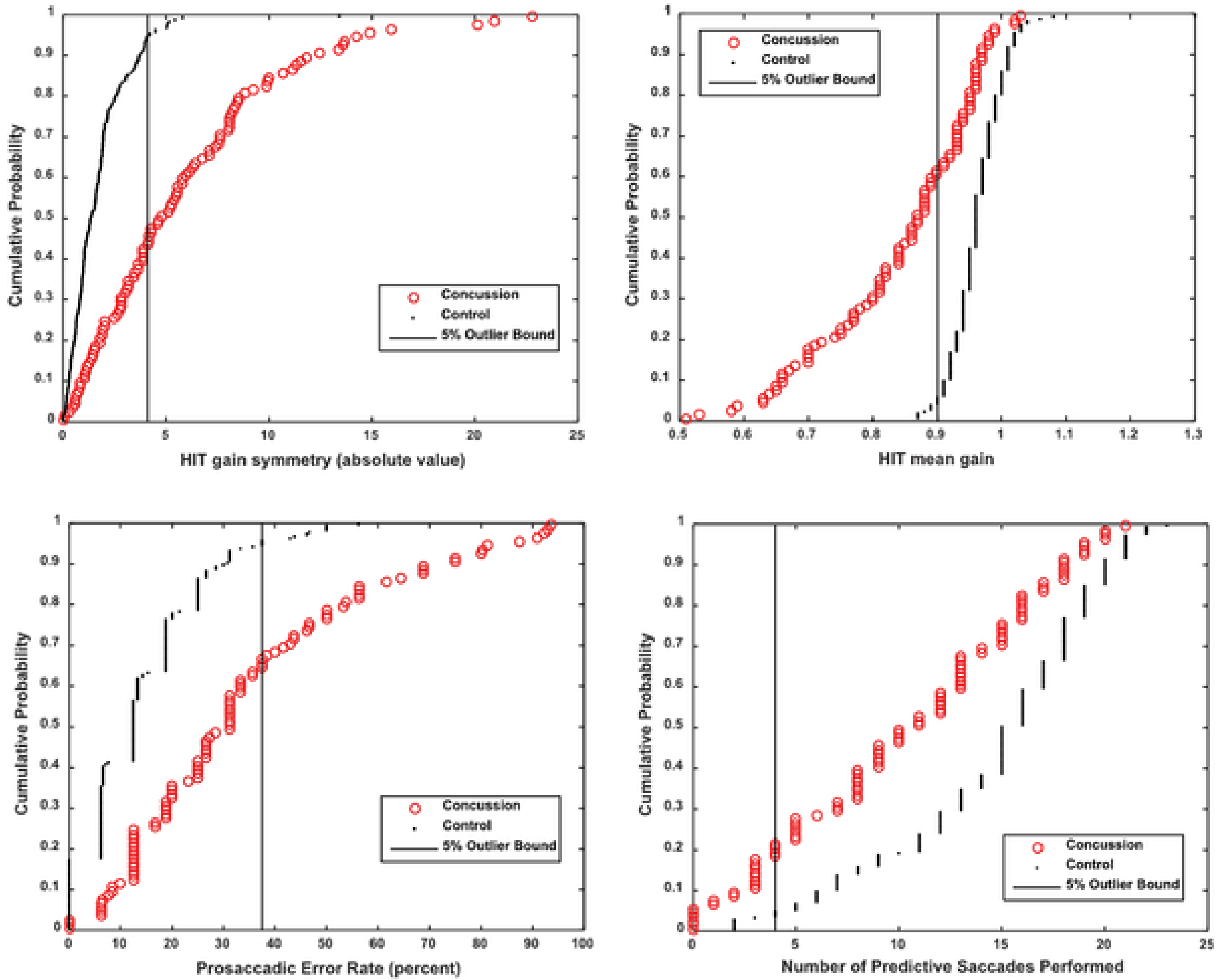

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Table 6. Prevalence of paired combinations of metrics outside the 95% control performance levels in subject with acute mTBI.

	crHIT gain symmetry	crHIT average gain	Predictive Saccades
Prosaccade error	19	25	9
crHIT gain symmetry		39	12
crHIT average gain			12

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Balaban C, Hoffer ME, Szczupak M, Snapp H, Crawford J, et al. (2016) Oculomotor, Vestibular, and Reaction Time Tests in Mild Traumatic Brain Injury. PLOS ONE 11(9): e0162168. doi:10.1371/journal.pone.0162168
http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0162168

Objective Assessment of Acute mTBI: Up to 2 Weeks Post-Injury

Laryngoscope Investigative Otolaryngology

The Use of Oculomotor, Vestibular, and Reaction Time Tests to Assess Mild Traumatic Brain Injury (mTBI) Over Time

Michael E. Hoffer, MD *; Carey Balaban, PhD*; Mikhaylo Szczupak, MD; James Buskirk, PT; Hillary Snapp, AuD; James Crawford, MD; Sean Wise, MD; Sara Murphy, MPH; Kathryn Marshall, PhD; Constanza Pelusso, MD; Sean Knowles; Alex Kiderman, PhD

NOTC Statistics

- Number of Concussed subjects: **106**
- Number of Control subjects: **300**
- Number of Testing sites: **2** **(**Naval Medical Center - San Diego & Madigan Army Medical Center)
- Sexes: Male (278 subjects) **68.47%**; Female (128 subjects) **31.53%**
- Age Groups: (18 to 21, 22 to 45)
- Age Groups and Sex: in 4 subgroups

Age Group	Sex	Controls		Session 1, Patients		Session 2, Patients		Session 3, Patients	
		n	% of total	n	% of total	n	% of total	n	% of total
18 to 21	Female	19	6.33%	9	8.49%	9	9.47%	9	10.59%
	Male	36	12.00%	25	23.58%	23	24.21%	22	25.88%
22 to 45	Female	76	25.33%	24	22.64%	20	21.05%	16	18.82%
	Male	169	56.33%	48	45.28%	43	45.26%	38	44.71%
Total		300	100.00%	106	100.00%	95	100.00%	85	100.00%

Time Interval Post Event

Gender	Session 1		Session 2		Session 3	
	Mean, days	SD	Mean, days	SD	Mean, days	SD
Female	2.93	1.84	9.44	3.01	16.68	3.28
Male	2.47	1.42	8.91	2.74	16.35	3.69
Average	2.62	1.58	9.09	2.83	16.47	3.53

Time Intervals by Days:

Session 1: 1.04 to 4.2 Days

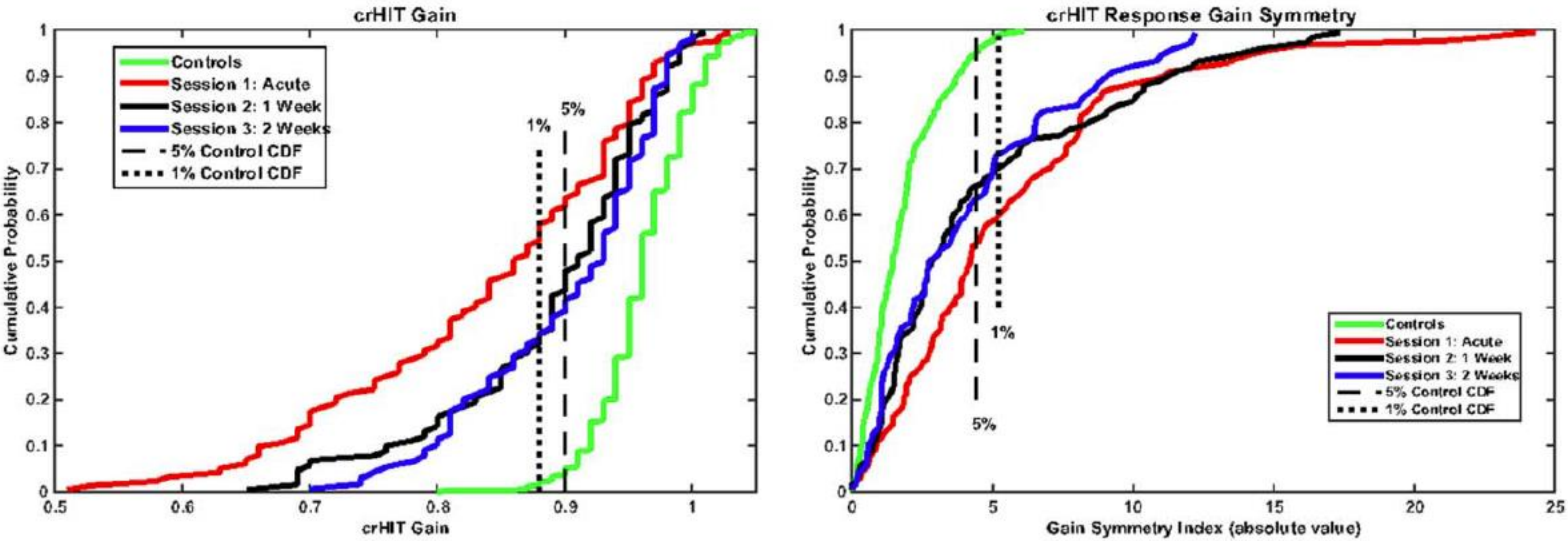
Session 2: 5.56 to 12.62 Days

Session 3: 12.94 to 20 Days

Subject Data

	Concussion Session 1		Concussion Session 2±		Concussion Session 3		No Concussion	
	Female (n=34)	Male (n=72)	Female (n=32)	Male (n=63)	Female (n=31)	Male (n=54)	Female (n=95)	Male (n=205)
Age	26.1 ± 6.1	26.2 ± 6.9					27.6 ± 6.9	27.3 ± 6.0
Symptom Severity Rating (SCAT2)	42.3 ± 24.9	42.5 ± 29.6	35.7 ± 26.9	29.5 ± 27.2	25.4 ± 25.7	23.9 ± 27.8	3.4 ± 6.5	2.6 ± 5.4
Time post-concussion (hr)	70.3 ± 44.3	59.3 ± 34.3	226.6 ± 72.3	213.9 ± 65.8	400.3 ± 78.6	398.3 ± 88.5		
FGA [≤22 fall risk]	25.1 ± 4.7 [5/34]	25.3 ± 4.6 [16/72]	26.5 ± 4.2 [2/32]	27.6 ± 3.3 [4/63]	28.1 ± 2.1 [1/31]	28.7 ± 2.1 [1/54]		
TMT A (sec)	32.4 ± 13.1	29.0 ± 10.7	22.7 ± 6.6	24.8 ± 13.3	20.1 ± 5.7	21.2 ± 12.4		
TMT B (sec) [norms: 49.8±12.5 sec]	52.5 ± 23.5	56.2 ± 23.7	45.1 ± 16.9	52.1 ± 22.9	37.9 12.9	43.1 ± 20.7		
DHI total [≥29 abnormal]	33.4 ± 22.3 [19/34]	30.4 ± 21.8 [30/72]	26.5 ± 23.0 [12/32]	22.1 ± 22.6 [21/63]	18.1 ± 21.9 [8/31]	17.6 ± 21.6 [13/54]		

Key Measure Changes Across Sessions



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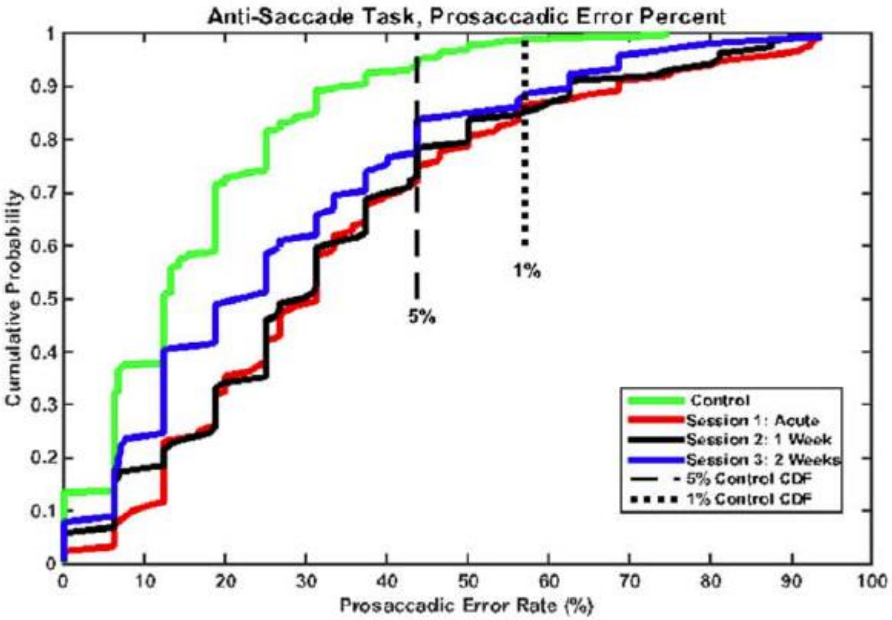

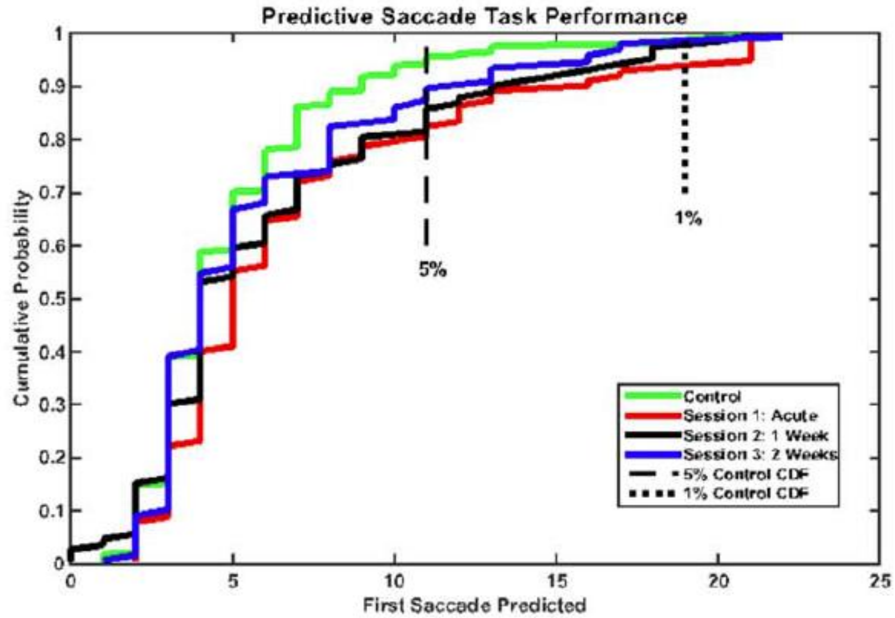

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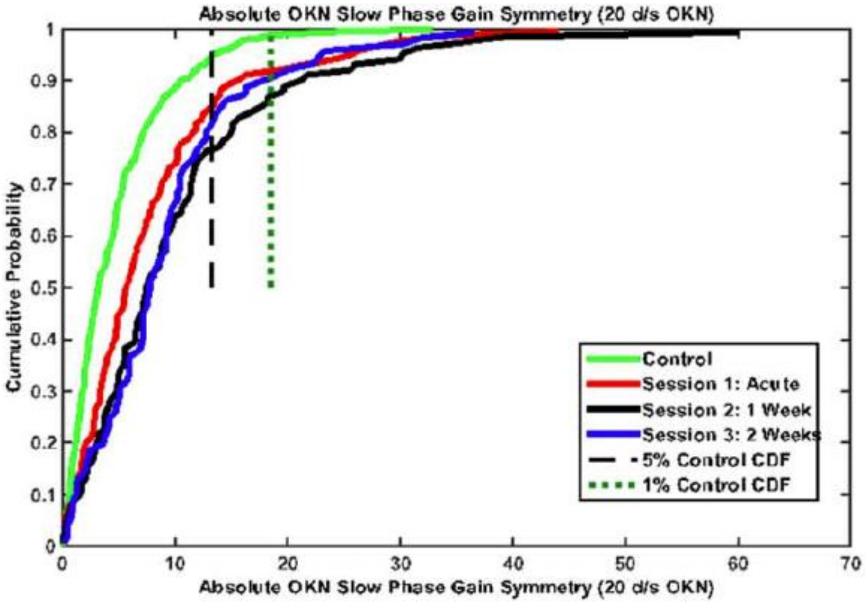
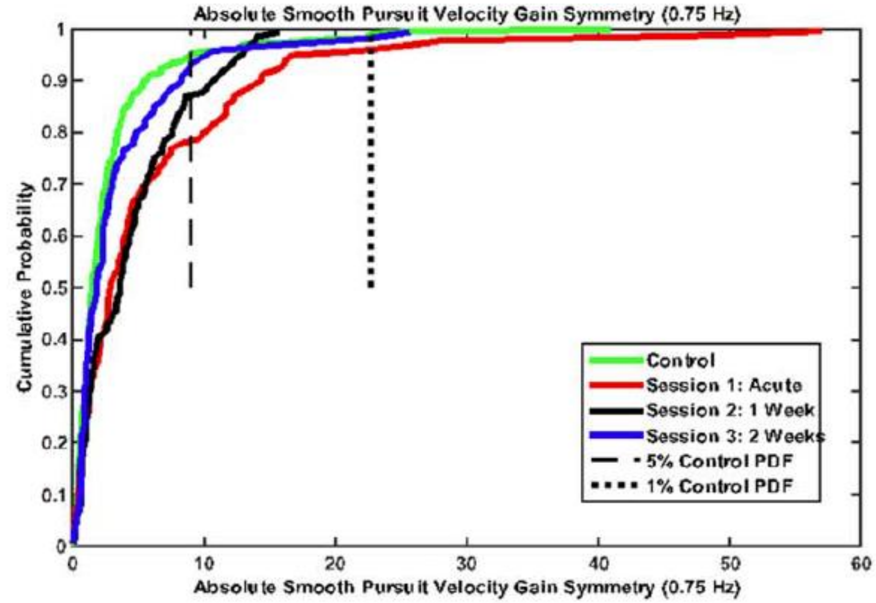




Proportion Outlier to Controls

5% and 1% tail outliers from controls entered	Session 1	Session 2	Session 3
crHIT average VOR gain	65/106 (61.3%) 54/106 (50.9%)	41/95 (43.2%) 28/95 (29.5%)	32/83 (38.6%) 25/83 (30.1%)
crHIT, absolute VOR gain Symmetry	49/106 (46.2%) 41/106 (38.7%)	32/95 (33.7%) 28/95 (29.5%)	31/83 (37.4%) 22/83 (26.5%)
Prosaccadic Error % in Anti-saccade Task	26/106 (24.5%) 14/106 (13.2%)	20/95 (21.1%) 14/95 (14.7%)	13/83 (15.7%) 10/83 (12.1%)
First Predicted Saccade	18/106 (17.0%) 6/106 (5.7%)	13/95 (13.7%) 2/95 (2.1%)	8/83 (9.6%) 1/83 (1.2%)
OKN Slow Phase absolute velocity gain symmetry (20 deg/s stimulus)	16/106 (15.1%) 9/106 (8.5%)	22/95 (23.2%) 12/95 (12.6%)	15/83 (18.1%) 8/83 (9.6%)
Horizontal Smooth Pursuit absolute velocity gain symmetry	23/106 (21.7%) 4/106 (3.8%)	12 (12.6%) 0	6 (7.2%) 1 (1.2%)

Post-concussion Improvement: 1 and 2 weeks

Classification Tables

Observed Acutely		Predicted: Concussion No	Predicted: Concussion Yes	Percentage Correct
Concussion	No	**295**	**5**	**98.3**
	Yes	**15**	**91**	**85.8**
Overall Percentage				**95.3**

Observed 1 Week Post-Concussion		Predicted: Concussion No	Predicted: Concussion Yes	Percentage Correct
Concussion	No	**295**	**5**	**98.3**
	Yes	**34**	**63**	**64.9**
Overall Percentage				**89.2**

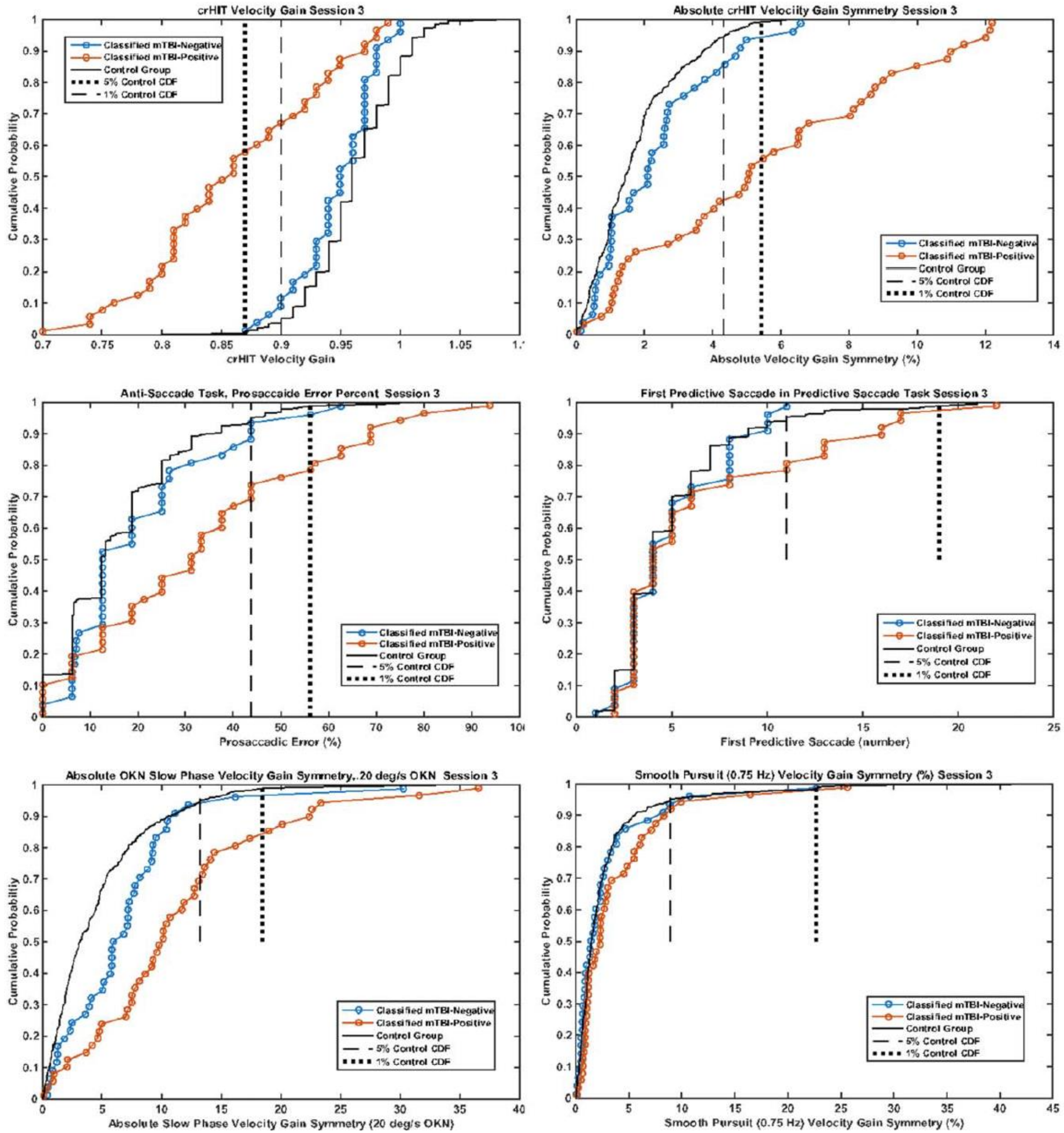
Observed 2 Weeks Post-Concussion		Predicted: Concussion No	Predicted: Concussion Yes	Percentage Correct
Concussion	No	**295**	**5**	**98.3**
	Yes	**41**	**42**	**50.6**
Overall Percentage				**86.9**

<u>ROC Analysis: Area Under Curve re: acute diagnosis</u>

Acute:	0.96 ± 0.01
1 Week:	0.86 ± 0.03
2 Weeks:	0.85 ± 0.03

<u>Key Variables</u>

- crHIT VOR Gain Average
- ABS crHIT VOR Gain Asymmetry
- Antisaccade, Overall Prosaccade Error, %
- Predictive saccade, first predictive;
- Magnitude of OKN Slow Phase Gain Asymmetry (20 d/s stimulus)
- . Magnitude of horizontal Smooth Pursuit Velocity Gain Asymmetry (0.75 Hz)



crHIT Velocity Gain Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
crHIT Velocity Gain
Absolute crHIT Velocity Gain Symmetry Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
Absolute Velocity Gain Symmetry (%)
Anti-Saccade Task, Prosaccaide Error Percent Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
Prosaccadic Error (%)
First Predictive Saccade in Predictive Saccade Task Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
First Predictive Saccade (number)
Absolute OKN Slow Phase Velocity Gain Symmetry,.20 deg/s OKN Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
Absolute Slow Phase Velocity Gain Symmetry (20 deg/s OKN)
Smooth Pursuit (0.75 Hz) Velocity Gain Symmetry (%) Session 3
Classified mTBI-Negative
Classified mTBI-Positive
Control Group
5% Control CDF
1% Control CDF
Cumulative Probability
Smooth Pursuit (0.75 Hz) Velocity Gain Symmetry (%)

Background

- Disconjugate eye movements (convergence and divergence) track objects that vary in depth over the binocular visual field. These eye movements can be measured objectively and are commonly affected following mTBI.

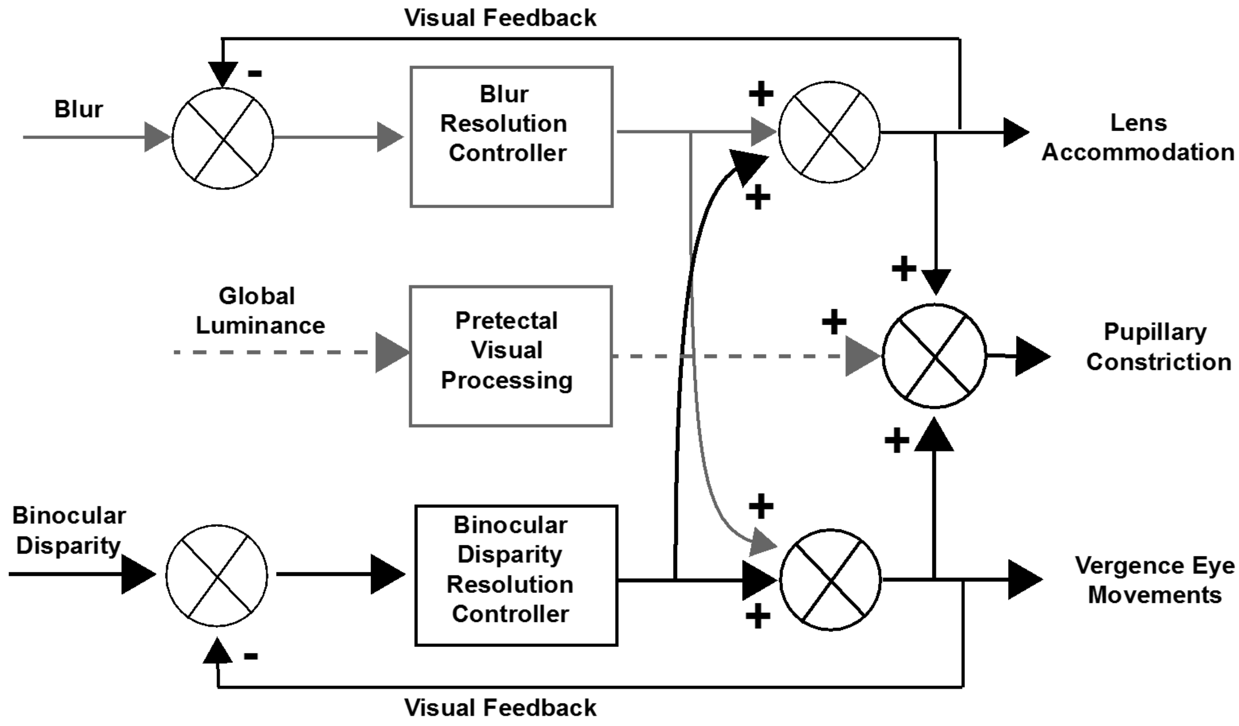
- Convergence insufficiency, determined by static measures of vergence function, has been associated with mTBI

  – Receded near point of convergence amplitude
  – Decreased compensatory fusional ranges at near distances
  – Abnormal phoria at near or far displacements (horizontal, vertical)

Vergence Eye Movements in TBI

- Thiagarajan P, Cuiffreda KJ, Ludlam DP. Vergence dysfunction in mild traumatic brain injury (mTBI): a review. Ophthalmic Physiol Opt 2011, 31: 456-468.
- Alvarez TL, Kim ET, Vicci VR, Dhar SK, Biswal BB, Barrett AM. Concurrent visual dysfunctions in convergence insufficiency with traumatic brain injury. Optom Vis Sci 2012, 89:1740-1751
- Tyler CW, Likova LT, Mineff KN, Elsaid AM, Nicholas SC. Consequences of traumatic brain injury for human vergence dynamics. Front Neurol 2015, 5:282

Coordinated Accommodation, Vergence, and Pupil Activity



Study Design

- mTBI subjects and controls were tested at three sites:
  - University of Miami Miller School of Medicine
  - Madigan Army Medical Center
  - Naval Medical Center San Diego

- All mTBI subjects were diagnosed by an emergency room physician

- mTBI subjects tested using the following time line

Control Subjects

- 36 male (69.2%), 16 female (30.8%)
  - Mean: 28.7 years
  - Range: 21 to 45 years
  - SD: 6.3 years

mTBI subjects

- 13 male (76.5%), 4 female (23.5%)
  - Mean: 29.1 years
  - Range: 20 to 43 years
  - SD: 8.1 years

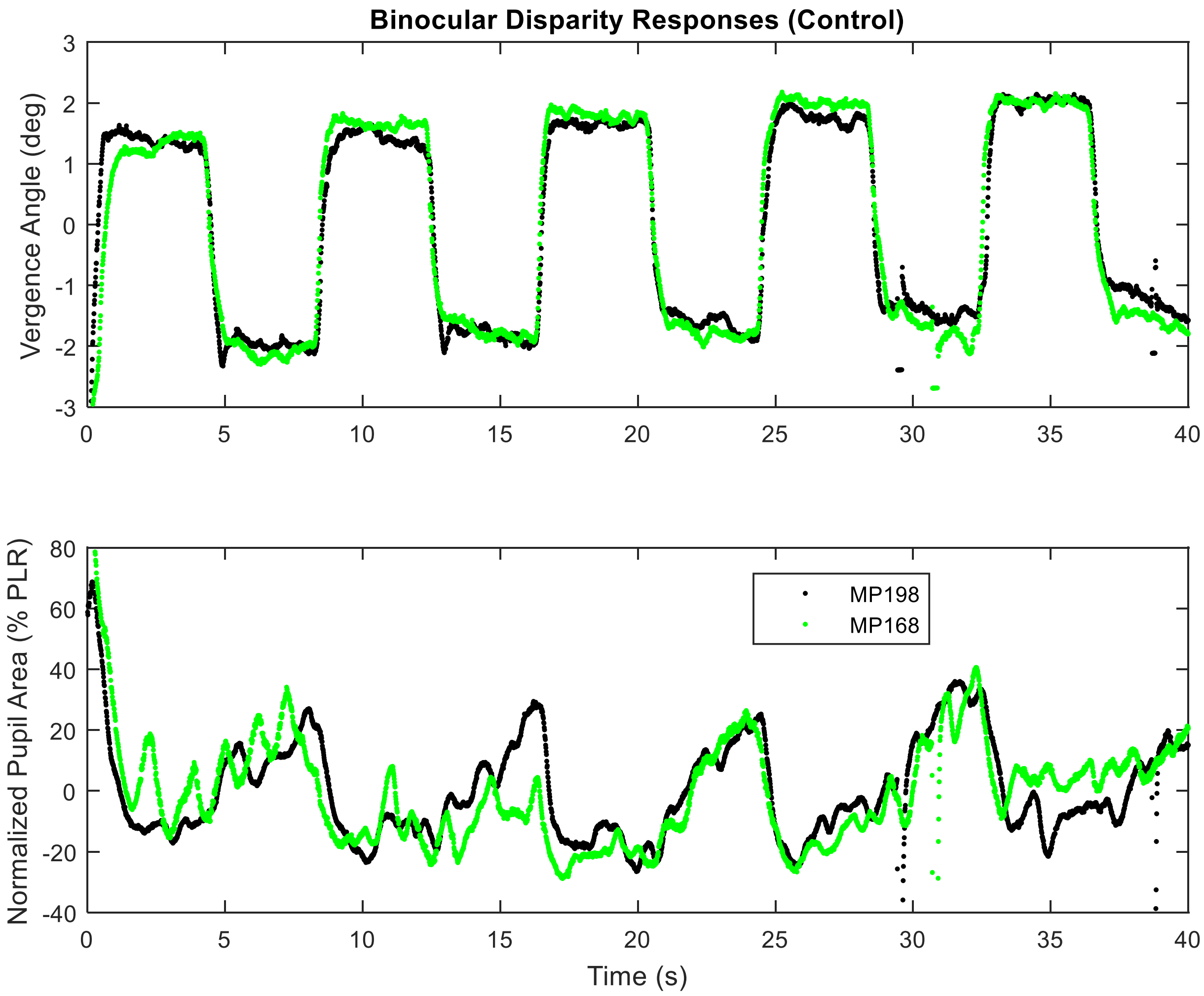
I-PAS Vergence Tasks

- Each eye viewed a white square with red center (0.1° visual angle)
  - Disparity fusion task: Disparity shifts in the horizontal plane equivalent to symmetric, approximately ± 1.4° vergence eye movement steps.
  - Disparity pursuit task: Sinusoidal convergence (toward nose) and divergence (laterally) movement in the horizontal plane equivalent to symmetric, approximately ± 2.5° vergence pursuit at 10 sec/cycle.

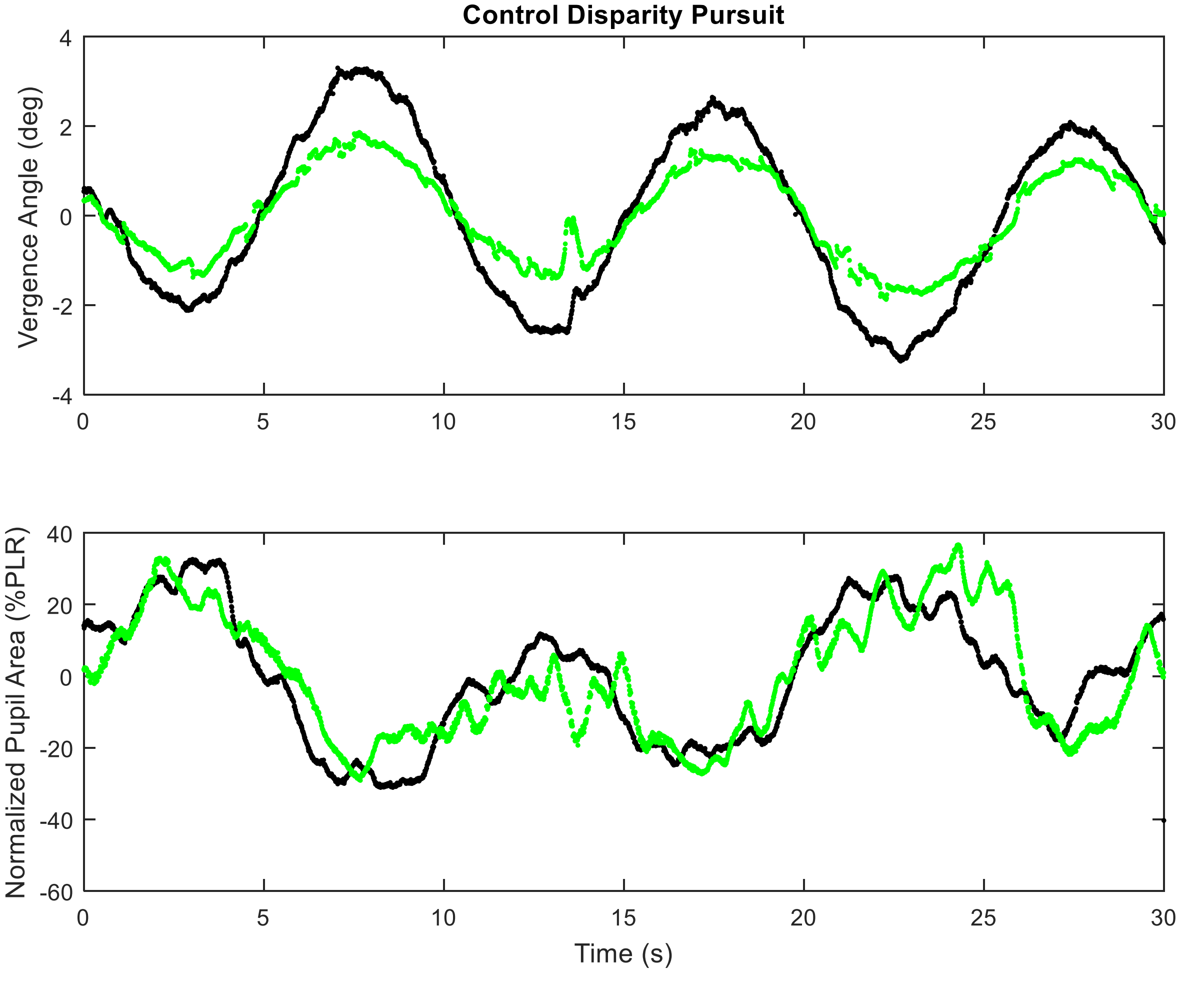
Data Analysis

- Pupillary light response test used to normalize pupil area
  - 0.42 to 65.4 cd/m^2 homogeneous illumination steps
- Vergence angle represented in degrees relative to zero at initial fixation

Control Subjects: Disparity Fusion Task



Control Subjects: Disparity Pursuit Task

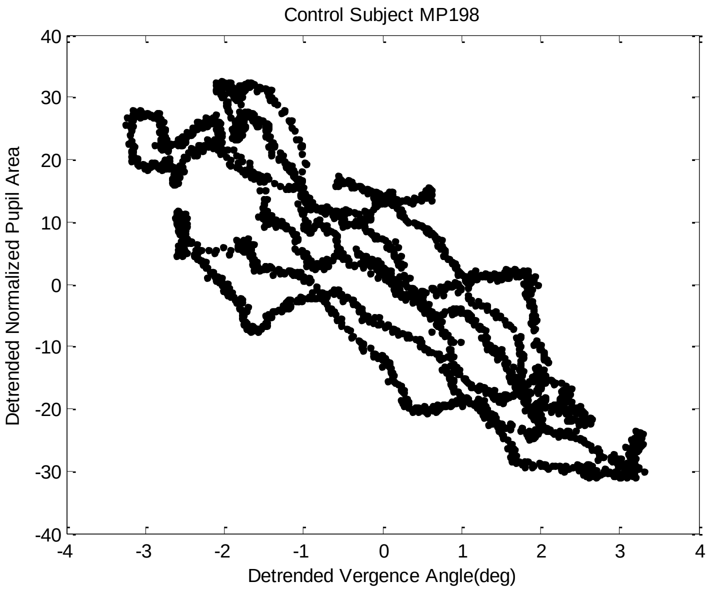


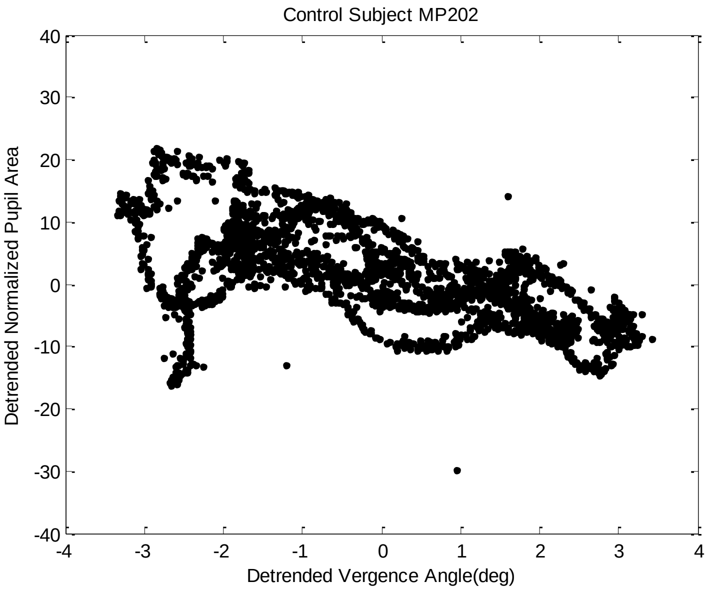
Half-Cycle Gains for Eye Movement and Pupil Components at 0.1 Hz

Session	N	Component	Direction	Magnitude (±SE)	R^2 (±SE)
Control	52	Vergence	Toward	2.537 ± 0.110°	0.933 ± 0.088
			Away	2.258 ± 0.100°	
		Pupil	Toward	23.538 ± 1.574%	0.563 ± 0.198
			Away	13.428 ± 1.955%	

Model: Least squares estimate of linear trend plus half cycle gains (toward and away)

Control Subjects: Variability Examples (Detrended Vergence-Pupil Coordination)

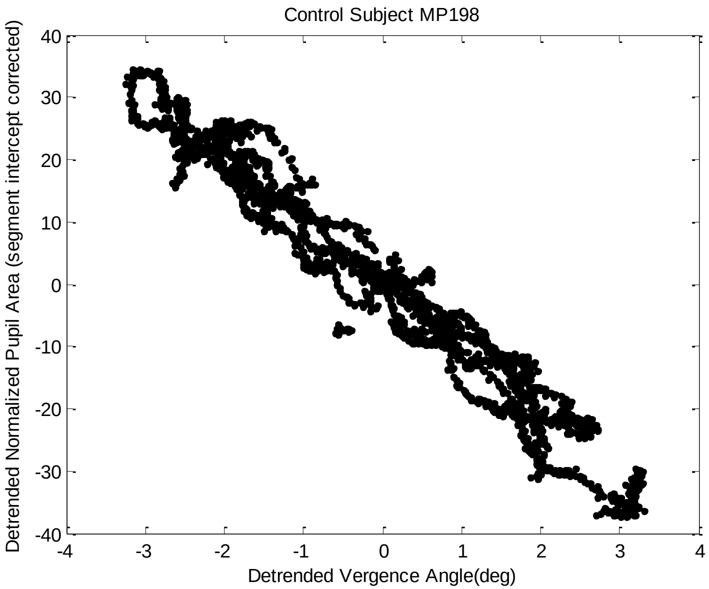




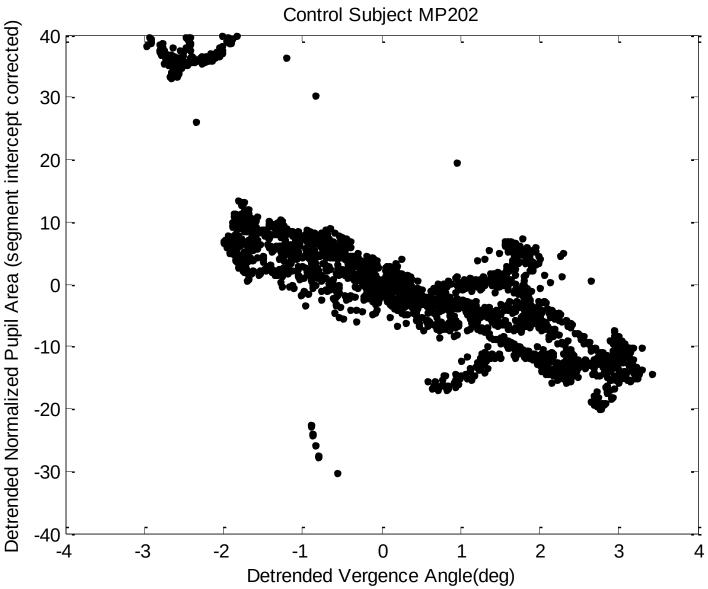
Piecewise Linear Analysis of Eye and Pupil Movement Coordination

- The sampled detrended normalized pupil area and detrended vergence angles are a multivariate time series
- A modified Gath-Geva clustering algorithm (Abonyi et al. Fuzzy Sets and Systems 149:39–56, 2005) was used for objective fuzzy segmentation of the time series into 15 segments with homogeneous properties.
  - Clustering algorithm for simultaneous identification of local probabilistic principal component analysis models
  - Based upon measured homogeneity of the segments and fuzzy sets used to represent the segments in time.
  - One principal component selected (represents the association between eye and pupil movements)

Plots After Subtraction of Linear Segment Intercept

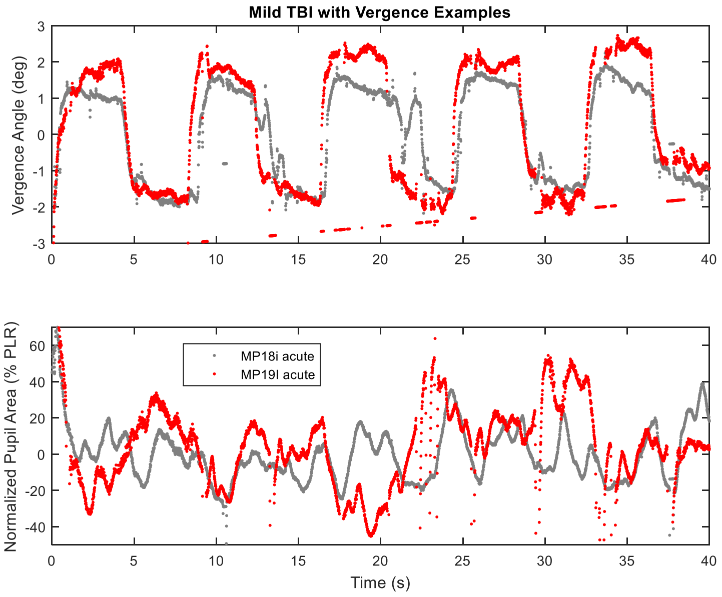


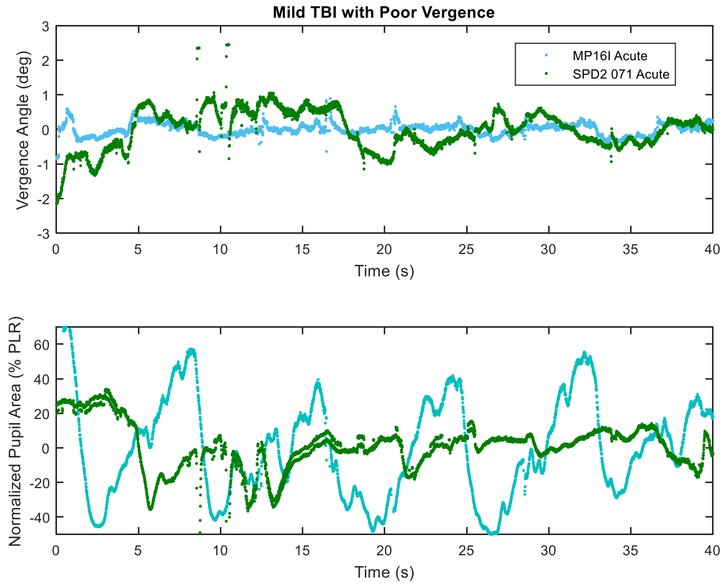
R^2=0.948



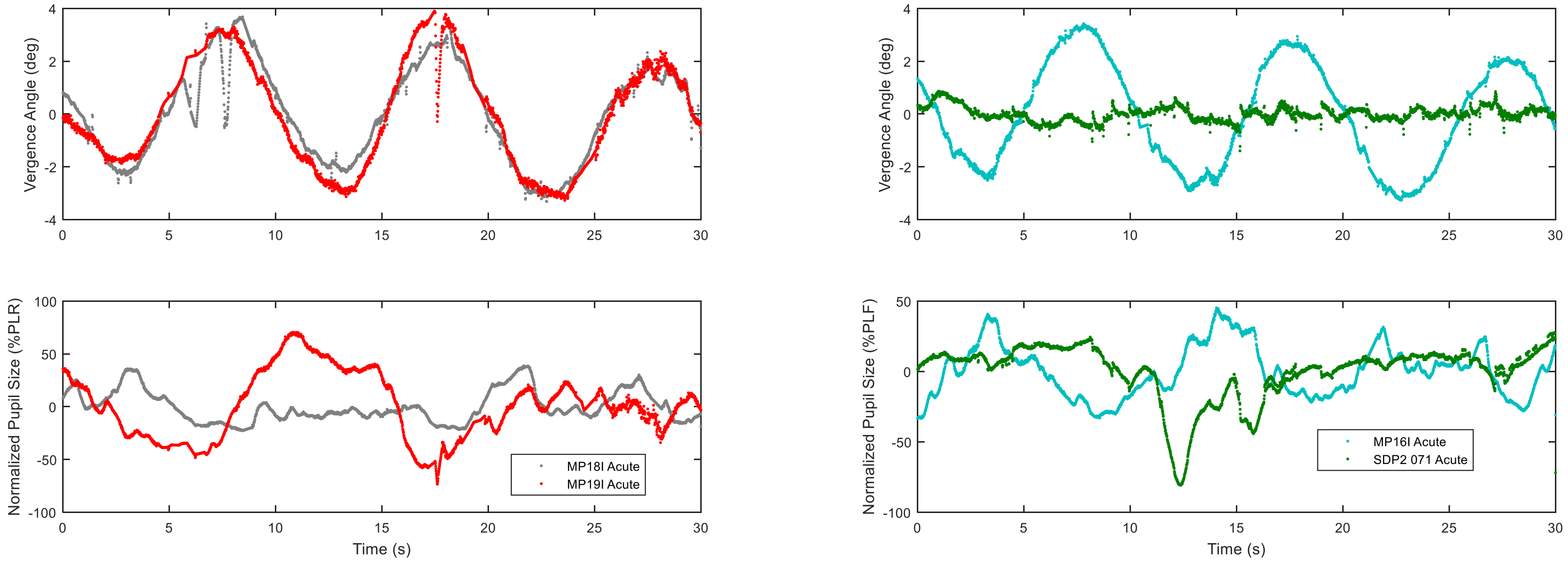
R^2=0.663

mTBI Subjects: Variability Examples (Detrended Data)

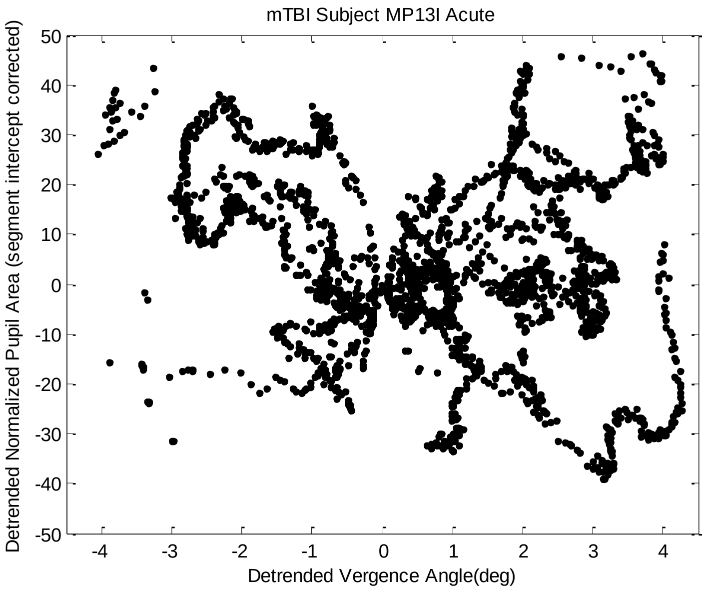


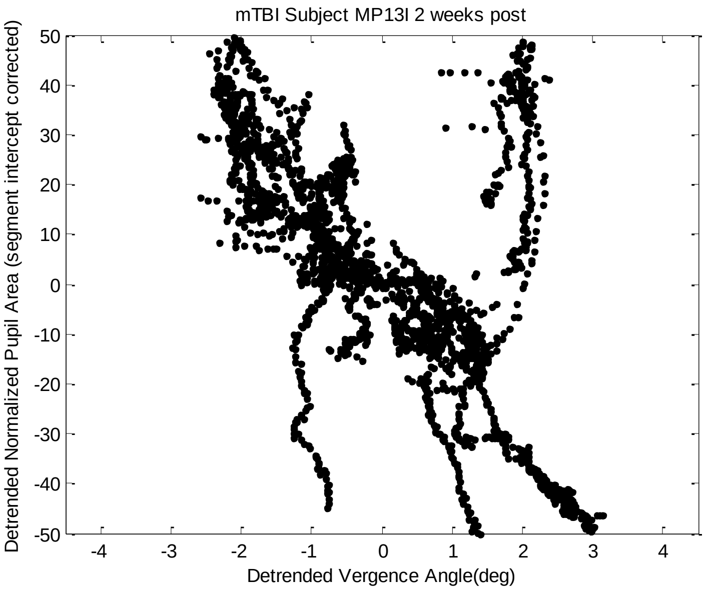


mTBI Subjects: Variability Examples (Detrended Data)



Plots After Subtraction of Linear Segment Intercept: mTBI example





R^2=0.195

R^2= 0.275

Eye and Pupil Movements
(Disparity Step Task)

Steady-State (static) Magnitude	Group	Converge (deg) or Constrict (%)	Diverge (deg) or Dilate (%)	Comment
Vergence Response	Control	1.40 ± 0.08 deg	1.44 ± 0.08 deg	mTBI < Control
	mTBI	0.68 ± 0.13 deg	0.60 ± 0.13 deg	
Pupil Response	Control	10.00 ± 0.97%PLR	7.60 ± 0.94 %PLR	mTBI < Control
	mTBI	4.90 ± 1.61%PLR	2.55 ± 1.56 %PLR	

	Group	Converge (deg) or Constrict (%)	Diverge (deg) or Dilate (%)	Comment
Vergence Tonic Gain	Control	1.409 ± 0.069	1.485 ± 0.071	mTBI < Control
	mTBI	0.620 ± 0.133	0.728 ± 0.138	
Pupil Gain (re: Vergence)	Control	5.032 ± 0.610	7.983 ± 0.595	NS (high variance)
	mTBI	-2.961 ± 4.005	-0.102 ± 3.679	

Eye and Pupil Movements

(Disparity Step Task)

- **Vergence and Pupil (Model) Delays are Altered During Acute mTBI**

	Group	Parameter Estimate	Comment
Vergence Delay (re: Stimulus)	Control	0.259 ± 0.015 s	mTBI > Control
	mTBI	0.327 ± 0.025 s	
Pupil Delay (re: Vergence)	Control	0.191 ± 0.024 s	mTBI < Control
	mTBI	0.078 ± 0.041 s	

Eye and Pupil Movements

(Disparity Pursuit Task, LS regression estimates)

Pursuit Task	Group	Converge (deg) or Constrict (%)	Diverge (deg) or Dilate (%)	Comment
Vergence Response	Control	2.54 ± 0.11 deg	2.26 ± 0.10 deg	mTBI < Control
	mTBI	1.75 ± 0.19 deg	1.86 ± 0.18 deg	
Pupil Response	Control	23.54 ± 1.57 %PLR	13.43 ± 1.96 %PLR	mTBI < Control
	mTBI	14.71 ± 2.75 %PLR	7.80 ± 3.42 %PLR	

Linear Segments Showing Vergence Angle-Pupil Area Slope

Mean ± Standard Error	Control (n=52)	Acute mTBI (n=17)	2 week post-mTBI (n=17)
Average Slope (and R^2) of Detrended Relationship; % pupil area per degree convergence (weighted by sample number)	-7.94 ± 0.59 (0.456 ± 0.031)	-5.26± 1.02 (0.234 ± 0.055)	-5.95 ± 1.17 (0.423 ± 0.063)
Proportion of Sample Points Showing Negative Linear Relationship	0.828 ± 0.015	0.729 ± 0.026	0.752 ± 0.029
Average slope (and R^2) of linear segments with negative slope (weighted by number of samples)	-13.28 ± 0.61 (0.660 ± 0.019)	-11.79 ± 1.07 (0.591± 0.033)	-12.91 ± 1.23 (0.682 ± 0.038)

Red denotes significantly different from Control by Tukey HSD tests

Conclusions

- In acute mTBI, a majority of patients showed
  - Depressed modulation magnitude and increased variability for ocular convergence (smooth pursuit)
  - Depressed modulation magnitude and increased variability of pupil constriction during convergence
  - Diminished coordination between the ocular convergence and pupil responses
- The performance recovered within 2 weeks in this small cohort of 17 mTBI subjects

Prospects for Operational Monitoring of Eye and Pupil Movements

- Pupil responses are sensitive to oxygenation status and altitude
  - Undersea hypoxia or hypercarbia
  - OBOG issues (include noise exposures)
- Unobtrusive interfaces with virtual and augmented reality platforms

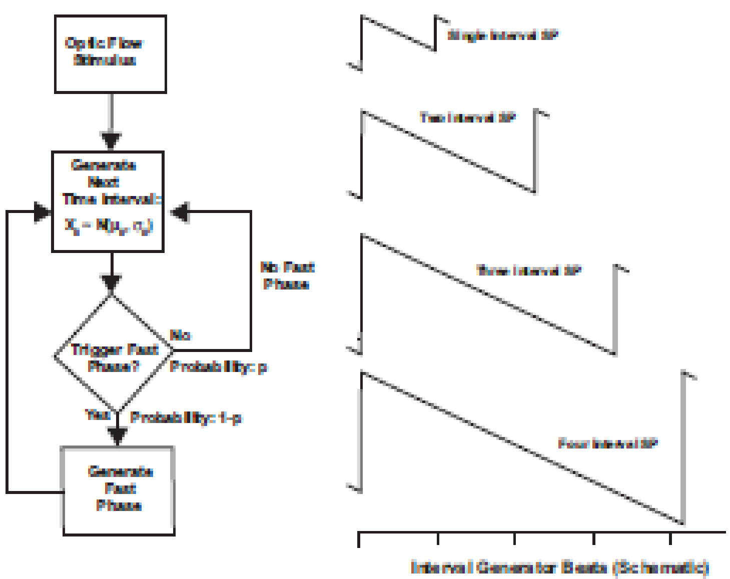
Timing of Eye Movements

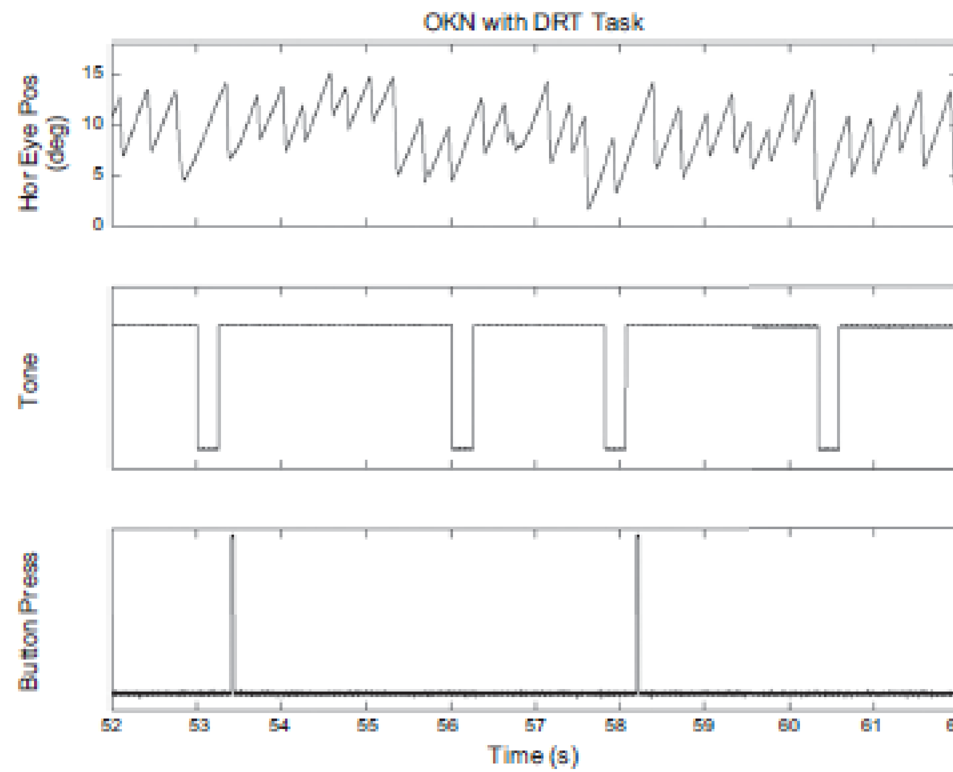
J Neurophysiol 117: 204–214, 2017.
First published October 19, 2016; doi:10.1152/jn.00342.2016.

RESEARCH ARTICLE | *Control of Movement*

Beat-to-beat control of human optokinetic nystagmus slow phase durations

Carey D. Balaban[1,2,3] and Joseph M. Furman[1,3,4]





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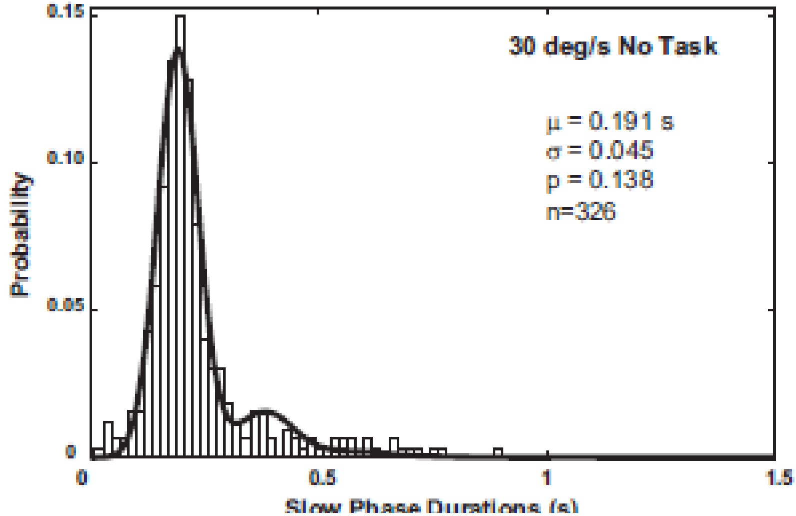
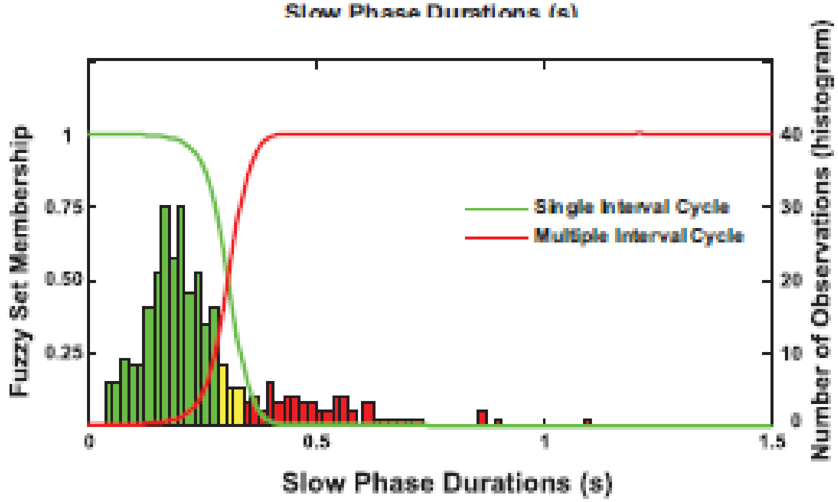
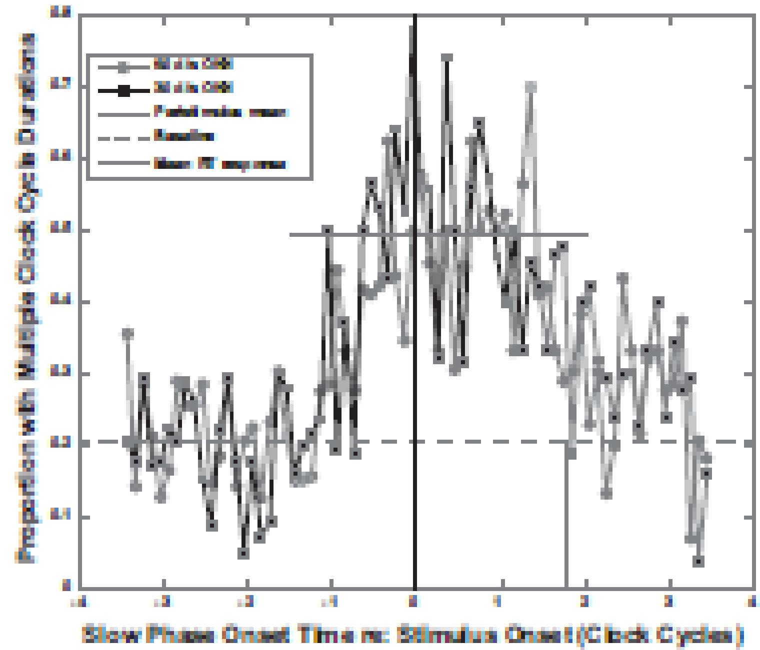






Technology Steps Forward

- Increase eye movement sampling rate to 1 kHz to accurately assess timing
- On-board, integral microprocessors for use in multiple platforms
- Wireless data communication

Intracranial Wave Guide, Resonance and Cavitation

Carey Balaban

Jeffrey Vipperman, George Klinzing, Brandon Saltsman

Biological Effects of Directed Energy

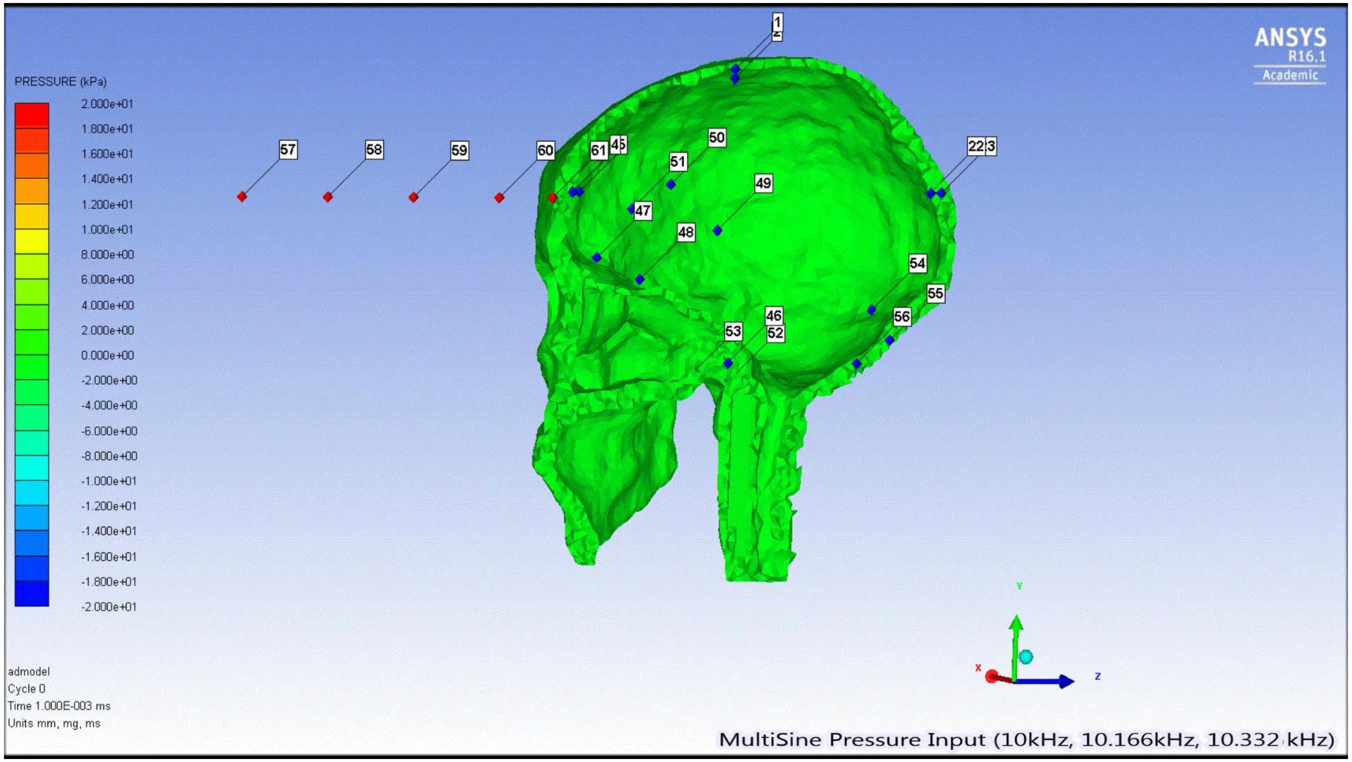
- Directed energy can produce peripheral and central neurosensory symptoms and signs
- Examples:
  - Occupational exposures
  - Environmental exposures
  - Military domain

New Project: ONR support

- Characterize wave guide, resonance and cavitation features of cranial contents
  - Blood vessels (surrounded by Virchow-Robin spaces) as coaxial fluid-filled wave guides and resonance cavities
  - Ventricles and cisternal system
  - Inner ear
  - Air spaces (sinuses, pharynx, etc.)

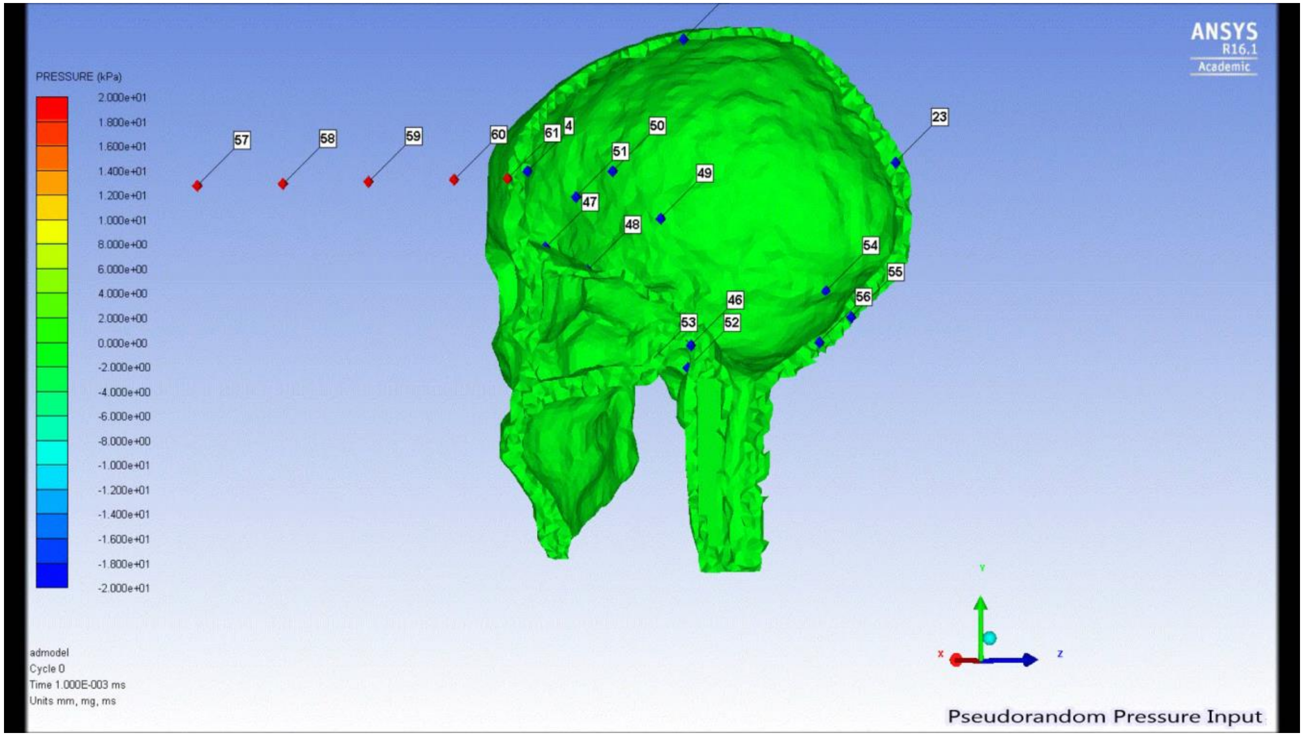
Integrated View

- Cranial resonances may differentially amplify incident energy



Integrated View

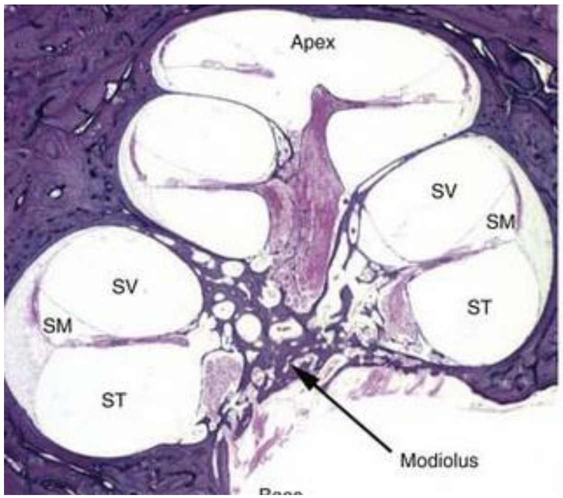
- Cranial resonances may differentially amplify incident energy

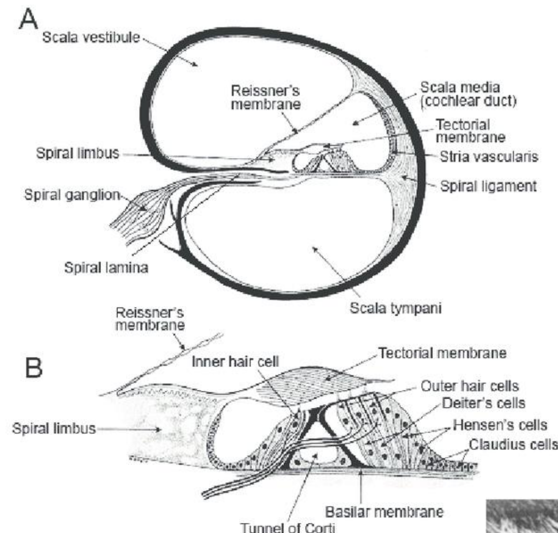


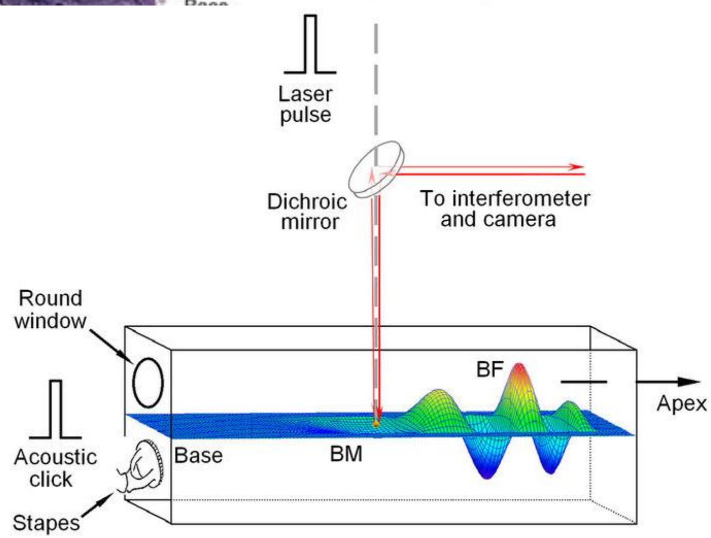
Georg von Békésy and Cochlear Transduction

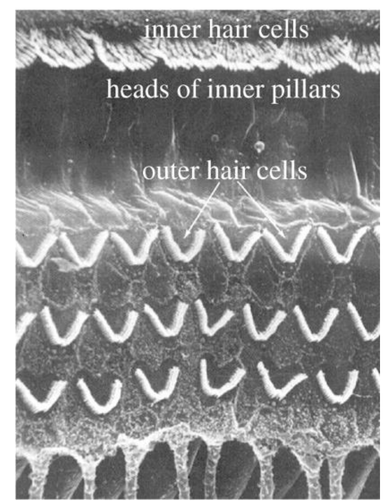
- Mechanical resonance of the basilar membrane
- Peak resonance of the basilar membrane varies from high frequencies at the cochlear base to low frequencies at the apex
- Activation of the regularly spaced sensory inner hair cells, and their relay to the auditory nerve axons, results in a tonotopic representation of narrowly tuned auditory nerve response units for processing incident sound

Classical Cochlear Mechanics



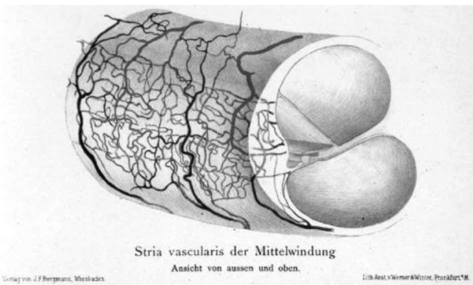


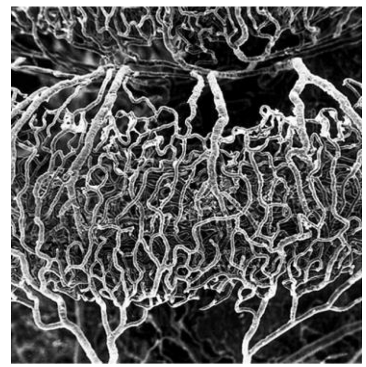




Stria Vascularis Structure

- Parallel network of capillaries, fed and drained at even intervals by arterioles and venules, in the lateral cochlear wall





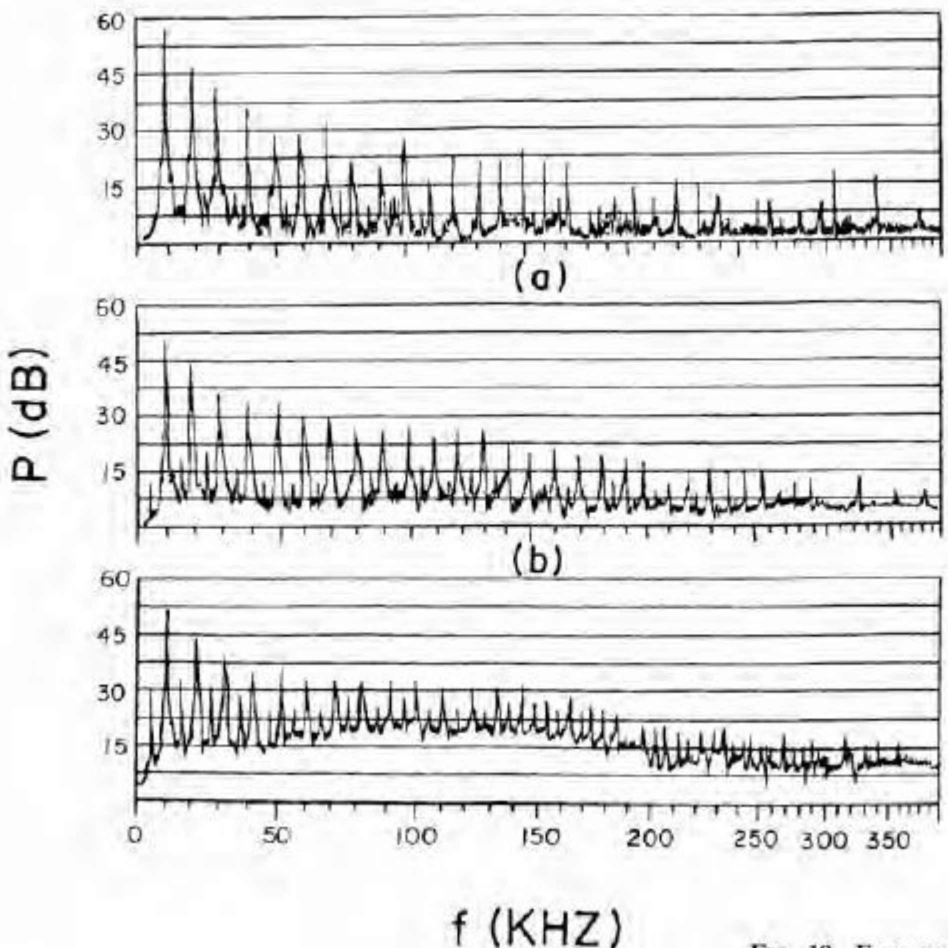
- Capillaries (12-16 µm diameter, 40-50 µm spacing)
  - Non-pulsatile flow
  - Packed tightly with blood cells for most of the length of the cochlea

Stria Vascularis Structure

- Vasculature structure differs in ‘hook portion’ of the basal cochlea in rodents
  - Locus of ultrasound activation of the basilar membrane
  - Separate (i.e., partially isolated) vascular network in this region does not appear to anastomose with the network in the remainder of the stria vascularis

    (Tange & Hodde ORL 47 (1985) 225-228).

Acoustic Cavitation



Edmonds PD (ed) Ultrasonics 1981

7. ACOUSTIC CAVITATION

By Robert E. Apfel

FIG. 10. Frequency spectrum from cavitation-produced acoustic emission in water. The driving frequency was 10 kHz and the peak acoustic pressures were (a) 0.4, (b) 0.6, and (c) 0.8 atm. With increasing amplitude, half harmonic multiples appear and nonperiodic noise is produced [L. Rosenberg (ed.), "High Intensity Ultrasonic Fields," p. 248. Plenum, New York, 1971].

Acoustic Cavitation

Ultrasound in Med. & Biol. Vol. 17, No. 2, pp. 179–185, 1991
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GAUGING THE LIKELIHOOD OF CAVITATION FROM SHORT-PULSE, LOW-DUTY CYCLE DIAGNOSTIC ULTRASOUND

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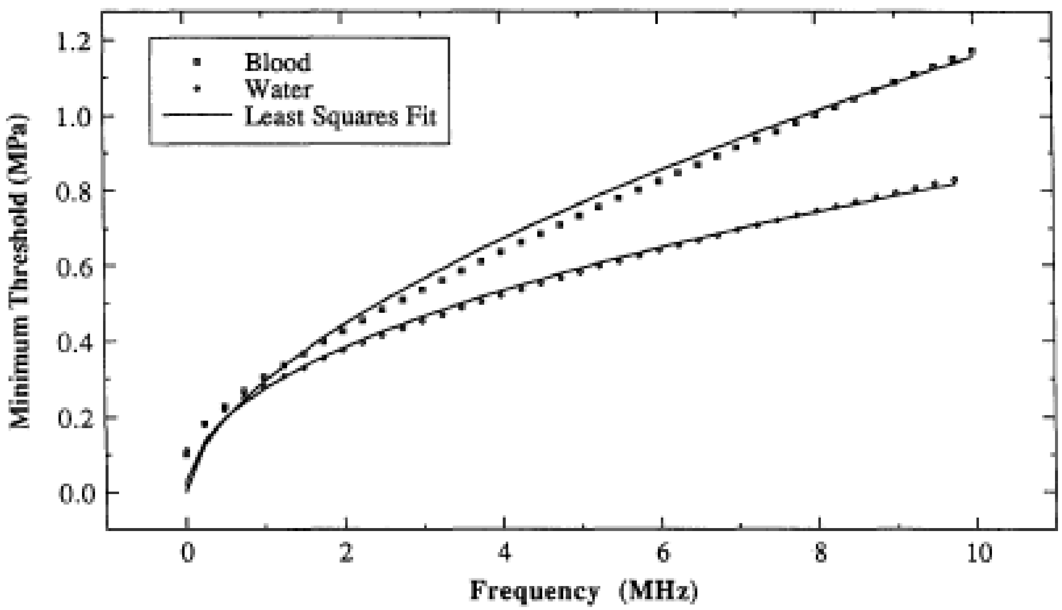

Fig. 2. Plot of the minimum cavitation threshold, P_{opt}, in water and in blood using the theory of Holland and Apfel (1989), assuming all nuclei sizes are present. Solid lines represent a least squares fit to the data of the form P^a/f = constant. The physical properties of the host fluids assumed for the calculations are as follows:

	Water	Blood
Density (kg/m^3)	1000	1059
Surface tension (kg/ms)	72×10^{-3}	56×10^{-3}
Viscosity (N/m)	1.0×10^{-3}	5.0×10^{-3}
Least squares fit of a	2.10	1.67

Energy Thresholds: Transfer to Cochlear Fluids

- Incident sound energy in the audible range produces considerable pressure differences in endolymph and perilymph compartments of the cochlear partition
- Published transfer functions are suitable for predictive modeling of cavitation
- Cavitation noise profiles can be measured directly

Intracochlear Energy Levels

Direct measurement of intra-cochlear pressure waves

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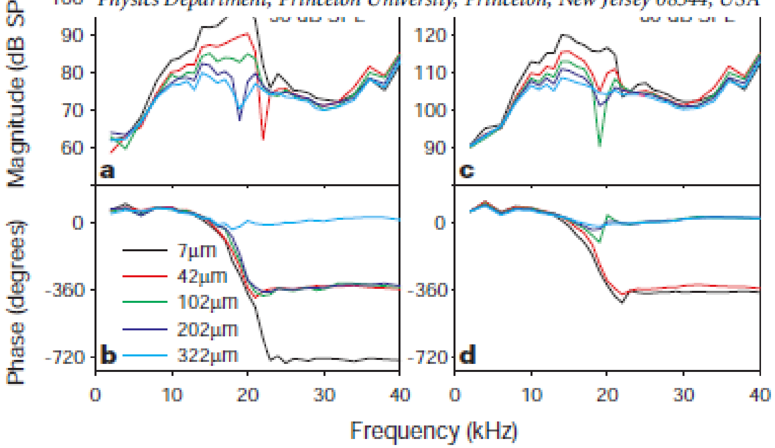

Figure 2 Scala tympani pressure versus frequency at the turn-one location. Each curve was measured at the distance from the b.m. indicated in the key. Pressure was also measured at 22, 62, 82, 122, 142, 162, 182, and 302 μm from the basilar membrane. **a**, **b**, Magnitude and phase, 50 dB SPL stimuli (as measured in ear canal); **c** and **d**, magnitude and phase, 80 dB SPL stimuli. Magnitude is expressed as SPL, defined as dB with respect to 20 μPa. The phase is referenced to the scala vestibuli pressure next to the stapes. (Scala tympani pressure with an accumulating phase such as that illustrated here has been measured in five basal and 13 turn-one experiments.)

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DOI: 10.1007/s10162-008-0150-y

Differential Intracochlear Sound Pressure Measurements in Normal Human Temporal Bones

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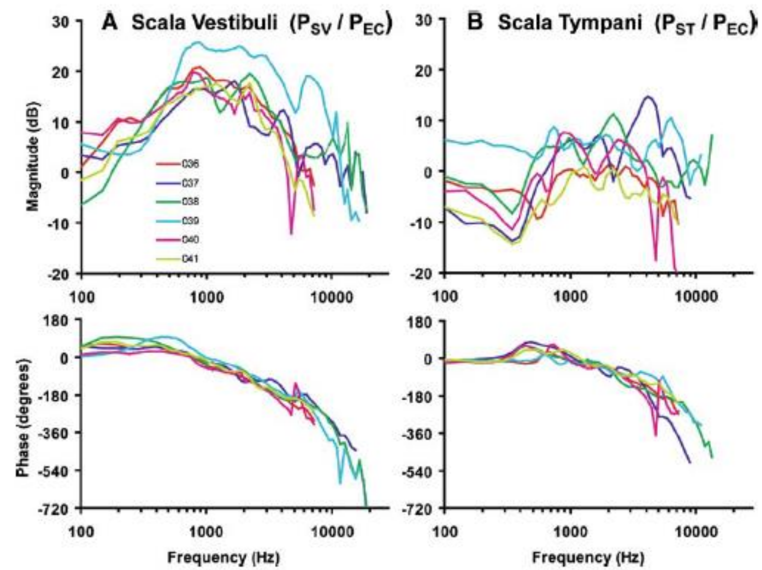
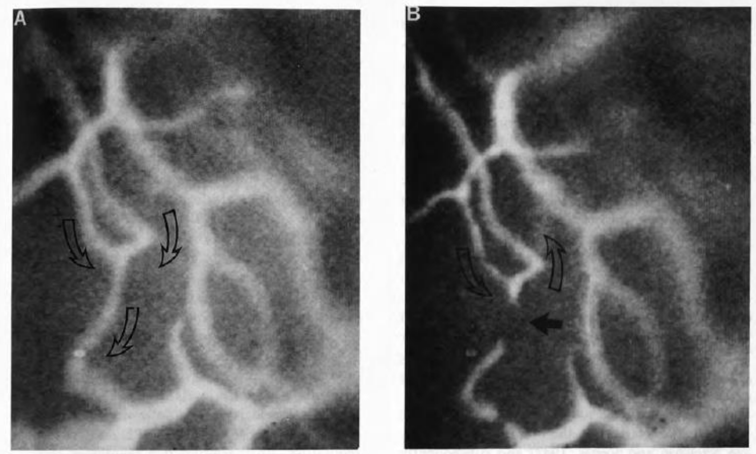


FIG. 2. Sound pressure (magnitude and phase) in **A** scala vestibuli and **B** scala tympani, normalized to the ear canal sound pressure, for six temporal bones.

Local Strial Blood Flow Altered During Sound Exposure



Hearing Research, 52 (1991) 217–224 217

HEARES 01525

Noise-induced changes in red blood cell velocity in lateral wall vessels of the rat cochlea

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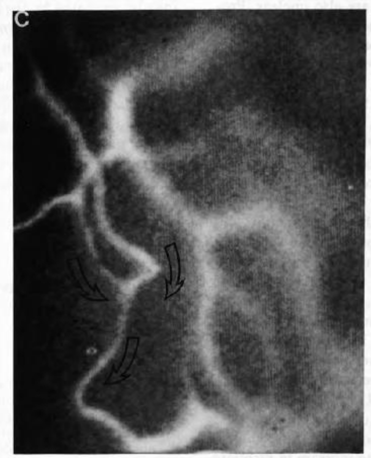

Fig. 3. This figure is a representative example of the effects of 110 dB broad-band noise on a group of stria vascularis vessels in a guinea pig cochlea. Photograph (A) depicts a pattern of flow prior to noise exposure. The direction of flow is denoted by the arrows.

Integrated View

- Cavitation of water and blood can occur in the audible frequency range at intensities produced in the cochlear fluids
- Pressures recorded in the cochlea during acoustic stimulation suggest that the threshold for blood cavitation is exceeded by several orders of magnitude at maximum resonance sites along the basilar membrane

Stria Vascularis Atrophy and Presbycusis

Laryngoscope, 1974

ATROPHY OF THE STRIA VASCULARIS, A COMMON CAUSE FOR HEARING LOSS.*†‡

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Laryngoscope 98: July 1988

ATROPHY OF THE STRIA VASCULARIS AS A CAUSE OF SENSORINEURAL HEARING LOSS*†§

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COCHLEAR PATHOLOGY IN PRESBYCUSIS

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Stria Vascularis Atrophy and Presbycusis

J Physiol 576.1 (2006) pp 73–86

Deafness in LIMP2-deficient mice due to early loss of the potassium channel KCNQ1/KCNE1 in marginal cells of the stria vascularis

Marlies Knipper[1], Cathrin Claussen[2], Lukas Rüttiger[1], Ulrike Zimmermann[1], Renate Lüllmann-Rauch[3], Eeva-Liisa Eskelinen[4], Jenny Schröder[2], Michael Schwake[2] and Paul Saftig[2]

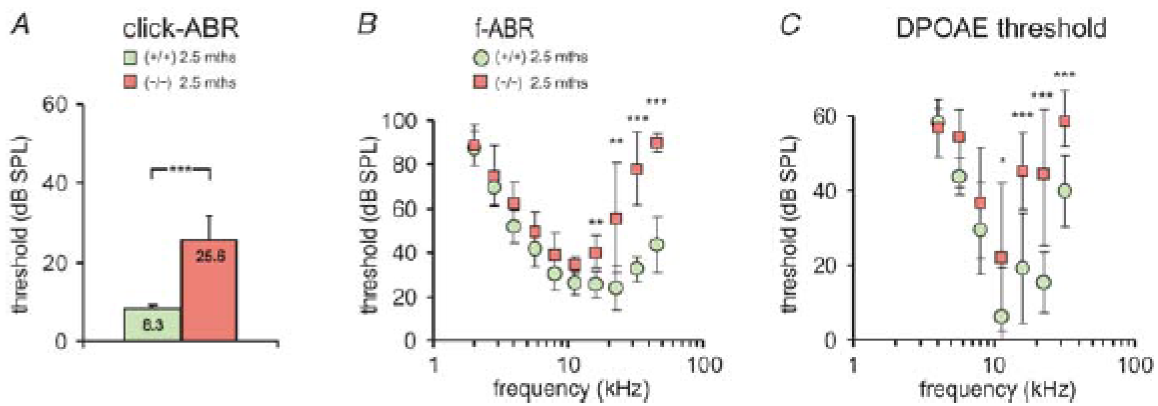

Figure 1. Hearing thresholds in LIMP2-deficient mice
ABR (*A* and *B*) and DPOAE (*C*) thresholds for wild-type (LIMP2$^{+/+}$, 2.5 months) and knockout mice (LIMP2$^{-/-}$, 2.5 months). Vertical bars give the standard deviations of the means. *A*, ABR thresholds on click stimulation, mean for wild-type and knockout mice ($n = 12$). The threshold loss of 15.7 dB is statistically significant (*t* test, $P < 0.0001$). *B*, ABR thresholds as a function of frequency for wild-type (LIMP2$^{+/+}$, circles, $n = 5$) and knockout mice (LIMP2$^{-/-}$, squares, $n = 6$) of 2.5 months of age. Knockout animals exhibit a statistically significant hearing loss of up to 46 dB at frequencies above 11.3 kHz. *C*, DPOAE thresholds (dB SPL) for wild-type (circles, $n = 8$) and LIMP2$^{-/-}$ mice (squares, $n = 11$), legend as in *B*. Again, a statistically significant threshold loss of up to 29 dB for knockout animals at high frequencies became evident (>8 kHz).

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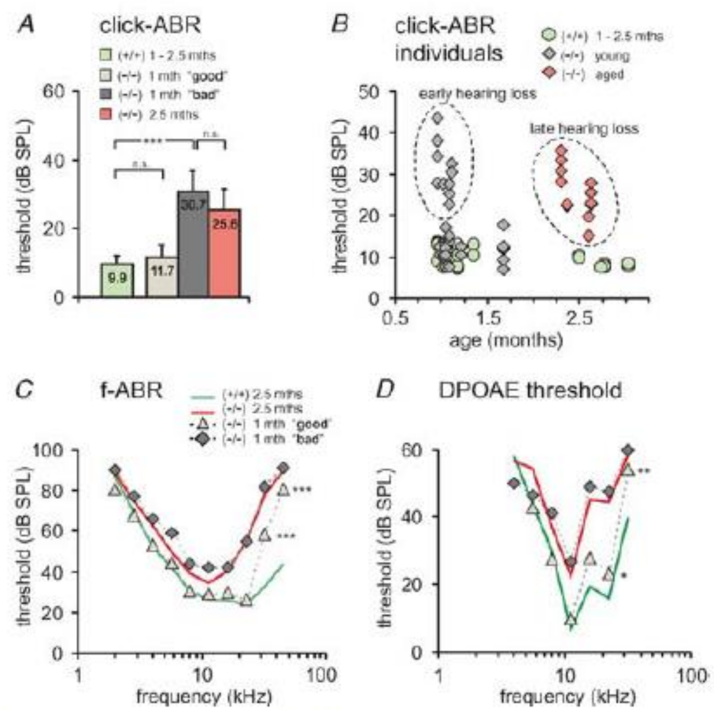


Figure 2. Early hearing impairment in LIMP2-deficient mice

Click-ABR thresholds (*A* and *B*), frequency-specific ABR threshold (*C*) and DPOAE threshold (*D*) of LIMP2$^{+/+}$ control mice and LIMP2$^{-/-}$ knockout mice of different ages. Mean (*A*, *C* and *D*) and individual data (*B*). *A*, knockout mice of 1 month of age (LIMP2$^{-/-}$, 1 mth) split into 2 groups of animals with hearing loss ('bad', dark grey) and animals without hearing loss ('good', light grey). Hearing of 'good' LIMP2$^{-/-}$ was not different from wild-type controls (LIMP2$^{+/+}$, 2.5 mths, green), and 'bad' LIMP2$^{-/-}$ was not statistically significantly different from LIMP2$^{-/-}$ of 2.5 months of age (red). Data for controls and LIMP2$^{-/-}$ aged 2.5 months were replotted from Fig. 1*A*. *B*, individual ABR thresholds on click stimulation illustrating the two groups of LIMP2$^{-/-}$ animals with an early ('young', grey) and a late ('aged', red) hearing loss (diamonds, encircled data points). At 2.5 months of age, all LIMP2$^{-/-}$ animals

Directions

- Data sufficient for conducting computational simulation studies to test the hypothesis that cavitation of (1) blood in the lateral wall vascular network and (2) endolymph and perilymph compartments have the potential to increase hearing sensitivity
- Physical models can be constructed with additive manufacturing methods
- Animal experimentation

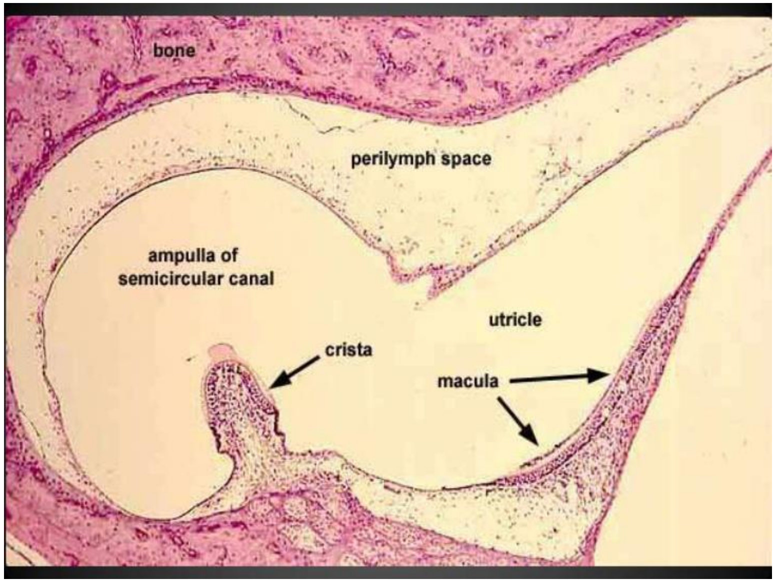
The Frey Effect

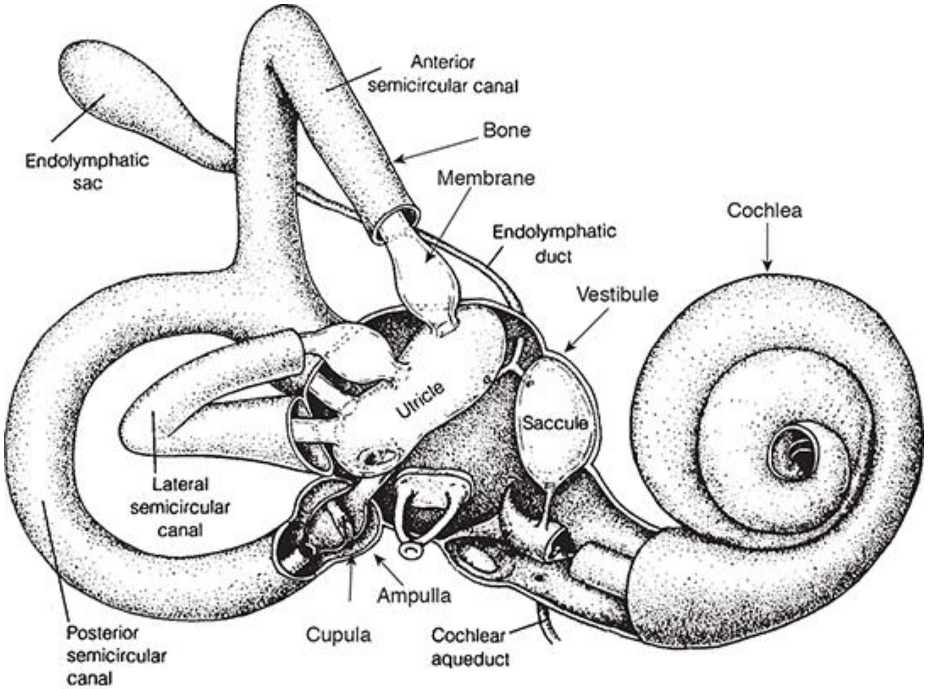
- Humans can 'hear' radar (microwave) emissions
- Chou et al (1975): Impulse exposures to microwave energy (for example, 918 MHz, 10 kW peak, 1-10 μsec duration) produced a 50 kHz microphonic potential in a guinea pig that outlasted the stimulus by more than 120 μsec
- Tyazhelov et al. (Radio Science, 14 (1979), 259-263): Human minimum detection thresholds for pulsed microwaves in the 10-15 kHz pulse repetition range

The Frey Effect

- A thermoelastic response of the inner ear was proposed for audibility of radar emissions
- Acoustic cavitation emissions from blood in the stria vascularis and fluids the inner ear (endolymph and perilymph) are one such plausible mechanism
- Question of effects on utricle and saccule (proximate to hook portion of cochlea)
- Intracranial blood vessels may also be affected?

Vestibule and Hook Portion





Source: Susan J. Herdman, Richard A. Clendaniel:
Vestibular Rehabilitation, 4th Edition:
www.FADavisPTCollection.com

Precision Medicine

- **Current clinical nosology as a clinical descriptive template**
  - **Symptoms**
  - **Signs**
  - **“Biomarkers”**
- **Establish etiologic nosology**
  - **Identify acute response processes**
  - **Identify longitudinal processes**
  - **Plan interventions appropriate to patients’ clinical trajectories**

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Evaluation of Neurologic Performance

- Tests were conducted using computer-controlled, earth-vertical axis rotational system, isolated from light and sound (I-Portal® NOTC, NKI Pittsburgh, PA)
- Eye data were collected using head-mounted goggle system with two 100 Hz infra-red cameras (I-Portal® 3.0, NKI Pittsburgh, PA).

- I-Portal® PAS (Portable Assessment System, with integrated head-mounted display and eye-tracking)